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THE UNIVERSITY OF ALBERTA

FREE RADICAL METHODOLOGY: ITERATIVE CYCLOPENTANNULATION AND FORMATION OF TRANS RING-FUSED COMPOUNDS

by

HARTFORD W. MANNING

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND

RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL 1992

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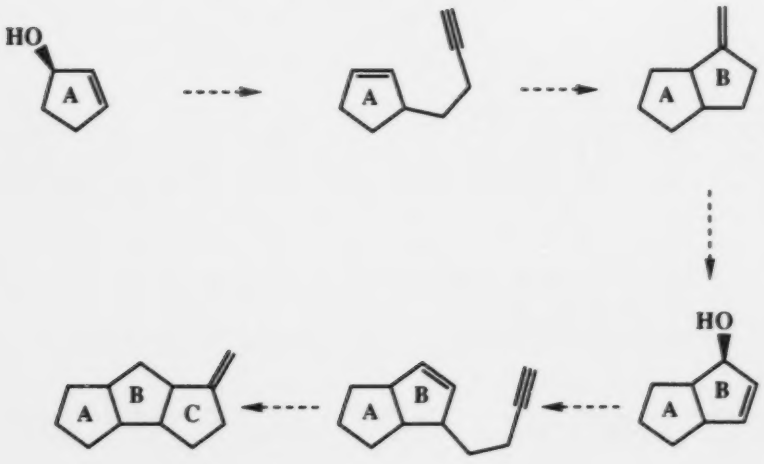
To my family and friends.

Abstract

This thesis describes the development of cyclopentannulation methodology using free radical techniques. Two aspects of the process have been addressed: The control of ring fusion geometry and the development of an iterative annulation procedure.

The first Chapter describes a method for preparation of polyquinane systems. This method is based upon a Claisen rearrangement-enyne radical cyclization sequence (Scheme A) which can be repeated after some simple functional group manipulations.

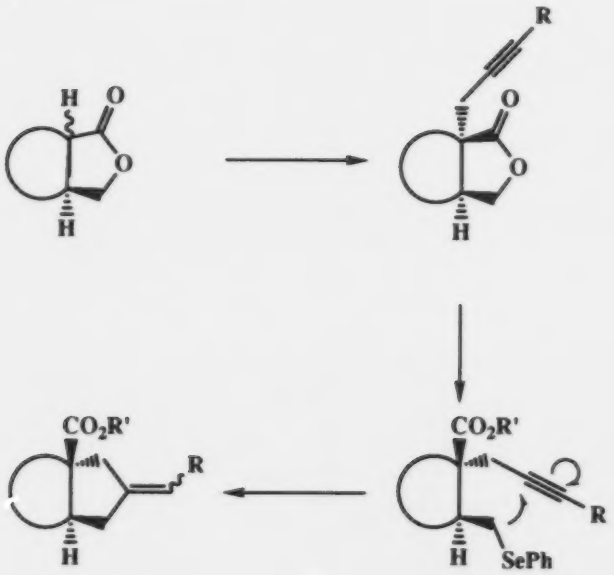
Scheme A



The second Chapter presents a method for controlling ring fusion geometry during the preparation of bicyclic

compounds. Trans ring-fused carbocycles are obtained by using a lactone-alkylation / ring opening sequence, as shown in Scheme B.

Scheme B



ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor D. L. J. Clive for his advice and encouragement during the course of my studies, and for his assistance in the preparation of this thesis.

The helpful assistance of the technical staff at the chemistry department is greatly appreciated and, I thank particularly the members of the NMR group for training on the high-field NMR spectrometers.

I gratefully acknowledge generous financial support in the form of scholarships from the Natural Sciences and Engineering Research Council of Canada, The Government of the Province of Alberta and the University of Alberta.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azoisobutyronitrile
Ar	aryl
Bn	benzyl
BOC	yield, based on conversion
bp	boiling point
br	broad (spectral)
Bu	butyl
d	doublet (spectral)
DCB	dicyclohexylborane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMThS	dimethylthexylsilyl
Et	ethyl
g	grams
h	hour
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrum
Hz	hertz
i-Pr	isopropyl
Imid	imidazole
J	coupling constant (in NMR)

KHMDS	potassium hexamethyldisilazane
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
M	moles per liter
μ	micro
m	multiplet (spectral), meter(s), milli
m/z	mass to charge ratio (mass spectrometry)
MCPBA	3-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
NMO	4-methylmorpholine *N*-oxide
nOe	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million (in NMR)
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
q	quartet (spectral)

rt	room temperature
s	singlet (spectral); second(s)
SET	single electron transfer
t	triplet(spectral)
t-Bu	tertiary butyl
TBDMS	tertiary butyldimethylsily
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

CHAPTER 1

FREE RADICAL METHODOLOGY: ITERATIVE CYCLOPENTANNULATION

I. INTRODUCTION

The use of free radicals in synthetic organic chemistry for the formation of carbon-carbon bonds is a valuable tool, as shown by the remarkable number of recent papers and excellent reviews.[1] The mildness of the reaction conditions and the normally high levels of their chemo-, regio- and stereoselectivity allow radical reactions to serve as powerful synthetic procedures whose applications complement those of their ionic counterparts.

This review will outline the basic chemical principles involved in radical cyclization and will then give an introduction to vinyl radicals, in which particular emphasis is placed on enyne cyclizations resulting from the intermolecular addition of stannanes to alkynes.

Basic Principles

The majority of free radical reactions which are of interest to the synthetic chemist are chain processes which may be divided into three discrete mechanistic stages: (1) radical initiation; (2) chain propagation; and (3) termination. Radical chain processes are attractive from a synthetic standpoint because they allow the controlled generation of the radicals themselves. Most free radicals are highly reactive species and, unlike anions or cations, they react with themselves by combination or

disproportionation at rates approaching the diffusion controlled limit.

Nearly all the useful reactions of free radicals can be grouped into three broad classes: (1) abstraction, (2) fragmentation, and (3) addition. Because addition processes involve formation of carbon carbon bonds, it is these reactions which have received the most attention. Free radical additions are recognized as powerful means for inter- and intramolecular carbon-carbon bond formation.

The effect of substituents on intermolecular radical additions has been comprehensively investigated by Giese.[2] The unique features of these reactions have made them useful in several natural product syntheses. The emphasis of this review, however, is on those radical additions which result in the formation of cyclic products.

Intramolecular Additions

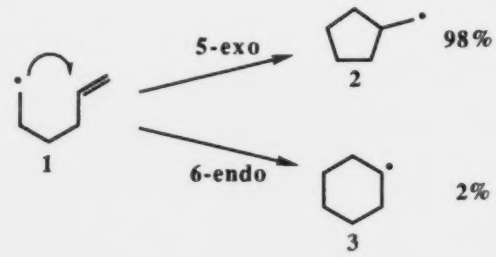
Ring closure reactions have received much synthetic attention and are most often applied to the preparation of five-membered rings. This is because cyclizations that generate five-membered rings are usually faster than for any other ring size. As a consequence they are least subject to the competitive formation of reduced and uncyclized products.

Regioselectivity

For the 5-hexenyl radical **1** there are two possible modes of ring closure, the 5-*exo* and 6-*endo* pathways (Scheme **1**).

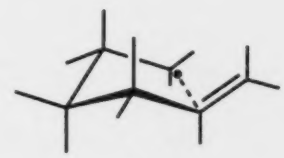
Although both are allowed by Baldwin's rules,[3] it has been found experimentally that a marked preference exists for *exo* ring closure.[4a] In the case of the parent 5-hexenyl radical,

Scheme 1



5-*exo* cyclization is 50 times faster than 6-*endo* closure even though a less stable primary radical is formed by the former path.

Beckwith and Ingold have stated that the preferential formation of the less stable cyclopentylcarbinyl radical occurs through a chair-like transition state (see **4**),[4b] and they indicate that radical ring closures are subject to



4

stereoelectronic and kinetic control. The course of the reaction is not determined by the thermodynamic stability of the product.[4c]

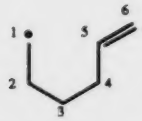
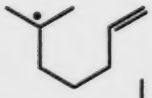
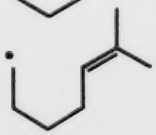
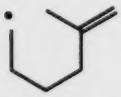
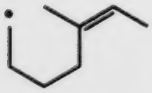
The chair-like transition state permits favorable overlap between the semi-occupied 2p (SOMO) orbital of the radical with one lobe of the vacant π^* (LUMO) of the olefin without producing the strain that would be generated by an *endo* approach.[4b,d] Unlike intermolecular additions, closure onto unactivated carbon-carbon bonds is facile and cyclizations involving polarized multiple bonds, e.g., CN and CO, are also possible.[4e,5]

Although there is an inherent preference for a 5-hexenyl radical to form a five membered ring, there are factors which can inhibit the 5-*exo* mode in favor of the 6-*endo* pathway. These factors include substitution at the proximal carbon, the presence of heteroatoms in the chain or sp^2 centers in the ring being formed, conformational restrictions due to the presence of other rings in the system, as well as stabilizing groups α to the radical.

Substitution in 5-hexenyl systems has a substantial effect on the regioselectivity of ring closure (Table **1**) and the preference for *exo* over *endo* closure can be reversed sterically.[4f] For 5-hexenyl radicals, alkyl substituents at the 1- or 6-positions have little effect on the rate or regiochemistry of ring closure. However, substitution at the 5-position can cause a preference for *endo* closure.[4b]

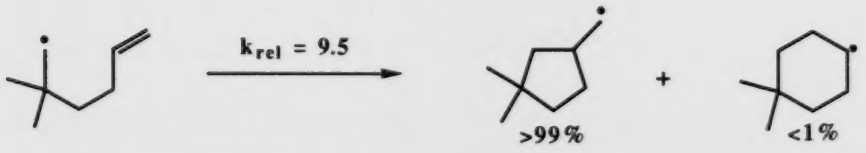
Substituents at the 2-, 3-, or 4-positions are found to enhance the cyclization rate and the Thorpe-Ingold or gem-dialkyl effect[6] has been used to explain this observation.

Table 1. Relative Cyclization Rates for Substituted Hexenyl Radicals

radical	k_{rel} exo	k_{rel} endo
	1.0	0.02
	1.4	0.02
	2.4	<0.01
	0.022	0.04
	0.022	<0.002

For example, the 2,2-dimethyl-5-hexenyl radical **5** cyclizes about 10 times faster then its unsubstituted analogue (Scheme **2**).[4c] Also the rate and regioselectivity of ring closure can

Scheme 2

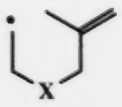


5 **6** **7**

be altered if the tether between the radical and the multiple bond contains a first-row heteroatom. For example, the 3-

oxa-5-hexenyl system undergoes ring closure much more rapidly than the parent 5-hexenyl analogue and displays a greater preference for *exo* closure. This is because the decreased path length, when the chain contains a heteroatom, increases the strain differences between *exo* / *endo* transition states such that even 5-substituted hexenyl radicals revert to predominant *exo* closure (Table **2**).[4c] The opposite situation

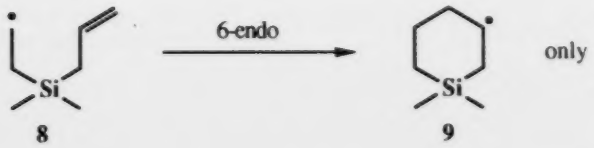
Table 2



X	k_{exo} / k_{endo}
CH_2	0.55
O	38.6

exists if a silicon atom is incorporated into the chain between the radical and the multiple bond.[7] The presence of the longer Si-C bonds lengthens the chain sufficiently to slow the rate of 5-*exo* closure. In the cyclization of the 3-sila-5-hexenyl radical **8** only the 6-*endo* product was observed (Scheme **3**).

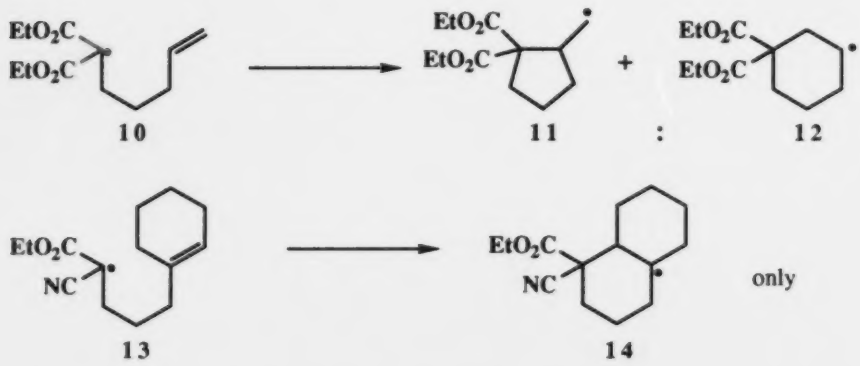
Scheme 3



8 **9**

The cyclization of doubly stabilized radicals (Scheme **4**) is reversible, thus allowing thermodynamically favored products to be formed or even to become the dominant

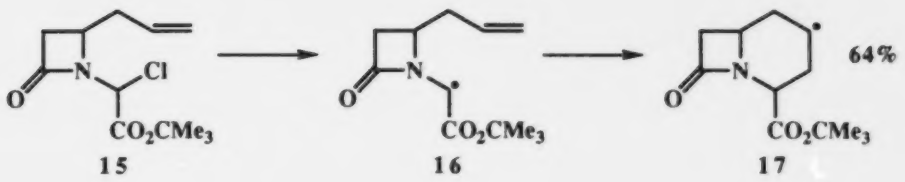
Scheme 4



products.[4d,8] The process then involves a thermodynamic equilibrium and becomes more important in cyclizations carried out at higher temperatures.

There are several other situations in which the formation of 6-*endo* products can compete or even dominate in cyclizations. If the pendants containing the radical precursor and acceptor are attached to another ring, the proportion of the 6-*endo* product is also sometimes increased.[9] An attractive route to bicyclic β-lactams **17** has been described by Bachi[9a] which has, as a key step, a 6-*endo* radical closure (Scheme **5**). It is suggested that the presence of the four-membered ring restricts the

Scheme 5

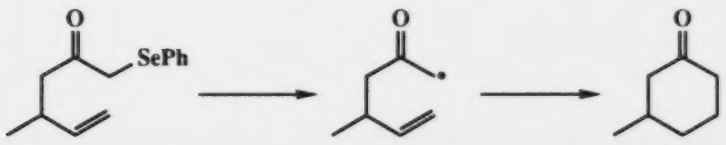


15 16 17

conformational freedom of the intermediate radical, thus disfavoring the 5-*exo* transition state. Formation of a five-membered ring would also generate a more strained product, and the presence of a stabilized electron-deficient radical probably also favors *endo* closure.

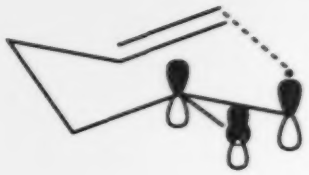
In contrast to the parent 5-hexenyl system, intramolecular cyclizations of α keto radicals with the carbonyl forming part of the ring, tend to close predominantly by the 6-*endo* pathway.[10] Cyclization of the α-keto radical **19** gives the cyclohexanone **20** in 76% yield (Scheme **6**). Houk has suggested that losses of resonance of

Scheme 6



18 19 20

the acyl radical and increased angle strain in the forming ring disfavor 5-*exo* closure (see **21**).[11]



21

The cyclization of vinyl radicals often gives products which appear to be the result of a 6-*endo* closure, and this type of cyclization will be discussed in more detail below (see Scheme **15**).

Stereoselectivity

The stereoselectivity that one can expect for intramolecular radical cyclizations of 5-hexenyl radicals can generally be predicted by using the Beckwith transition state model.[12] According to this model, the early transition state of a 5-*exo* cyclization resembles a cyclohexane ring (see **22**) which prefers the chair over the boat form, and the substituents on the ring prefer to be pseudoequatorial rather than pseudoaxial. The following guidelines result:

(1) Substitution at C-1 or C-3 of the 5-hexenyl radical gives primarily *cis*-disubstituted cyclopentanes, whereas substitution at C-2 or C-4 gives primarily *trans*-disubstituted cyclopentanes.

(2) Stereoselectivity is highest for C-1 and C-4 substituted systems.

22

There are, however, exceptions to these guidelines, the most important being in systems which afford bicyclic products.

Other Ring Sizes

The cyclization of 3-butenyl radicals is also known; however, the products are subject to rapid reopening due to ring strain and cyclized products can only be isolated in constrained systems (Scheme **7**).[13a]

The reverse reaction, ring opening of cyclopropylcarbinyl radicals does have synthetic applications.[13b,c]

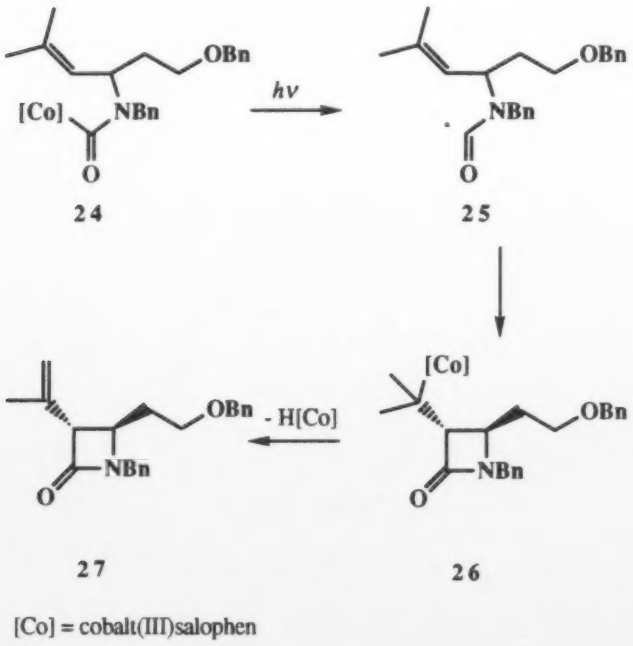
Scheme 7

22 23

Radical cyclizations of the 4-pentenyl system are rare. *Exo* closure is thermodynamically disfavored due to developing ring strain while the stereoelectronic requirements necessary for *endo* closure are prohibitively difficult to overcome.

There are, however, some recent reports of β-lactam synthesis involving 4-*exo* cyclizations.[14] Pattenden has synthesized (±)-thienamycin using a cobalt-salophen mediated radical

Scheme 8



cyclization. Photolysis of the acylcobaltsalophen **24** generates radical **25** which cyclizes onto the suitably located double bond. Loss of H[Co] from **26** provides the β-lactam **27** (Scheme **8**).

For larger ring sizes the increased chain length affords sufficient flexibility so that the difference between the extent of SOMO-LUMO overlap in the *exo* vs *endo* transition states is less. The result is a decrease in

regioselectivity. Cyclizations forming larger rings are also slower and therefore competing side reactions become important. A particular problem in the cyclization of 6-heptenyl radicals **28** is the 1,5-hydrogen abstraction giving stable allylic radicals **29** (Scheme **9**).[15] This side reaction

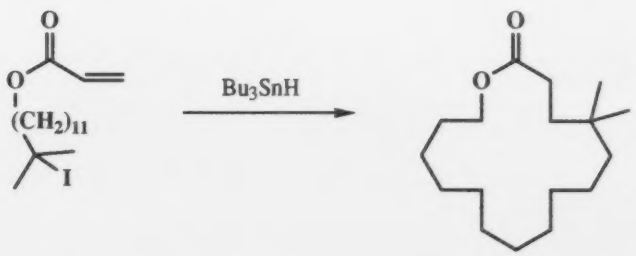
Scheme 9

28 **29**

can be eliminated in certain instances by substitution of the allylic position[16] or by activating the olefin.[17]

Porter has described radical ring closures forming macrolides of 11-20 atoms (Scheme **10**).[18] At these chain lengths the systems behave like intermolecular reactions with regiochemical control being determined by steric and electronic effects.

Scheme 10



30 **31**

Vinyl Radicals

A significant limitation to radical cyclizations is that the ring forming process often results in a decrease in the functional complexity of the starting material. This is especially true in the cyclization of alkyl radicals onto carbon-carbon double bonds. Vinyl radical cyclization has the chemically valuable feature that the product has a double bond in a predetermined position. Vinyl radicals are also more reactive than related alkyl radicals[19] and so vinyl radicals often provide better ratios of cyclic to reduced products than related alkyl radicals. Because of these features vinyl radicals are emerging as valuable intermediates in synthesis.[20] Much of the preliminary work using vinyl radicals was developed by Stork.[21,22]

The classical method for generation of vinyl radicals involves reaction of a vinyl halide with a stannane (Scheme **11**). The barrier for inversion of vinyl radicals is low

Scheme 11

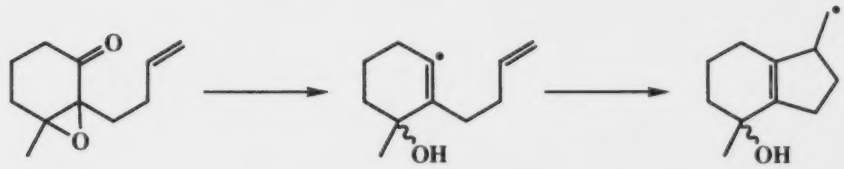
32 **33**

and, therefore, the geometry of the starting halide is not important for subsequent cyclization to be successful.[22a]

Because of the increased strength of sp^2 C-X bonds, the generation of vinyl radicals with trialkyl- or triaryltin radicals is restricted to vinyl bromides and iodides.[23] This has led several groups to search for alternate means to generate vinyl radicals.

Vinyl radicals have been proposed as intermediates in the Wharton reaction,[24] which is normally used to convert epoxy ketones into allylic alcohols. For example, treatment of oxirane **34** with an excess of hydrazine in methanol results in cyclization via vinyl radical **35** (Scheme **12**).[25] The

Scheme 12



34 **35** **36**

generation of vinyl radicals using this procedure, however, appears to be of limited use.

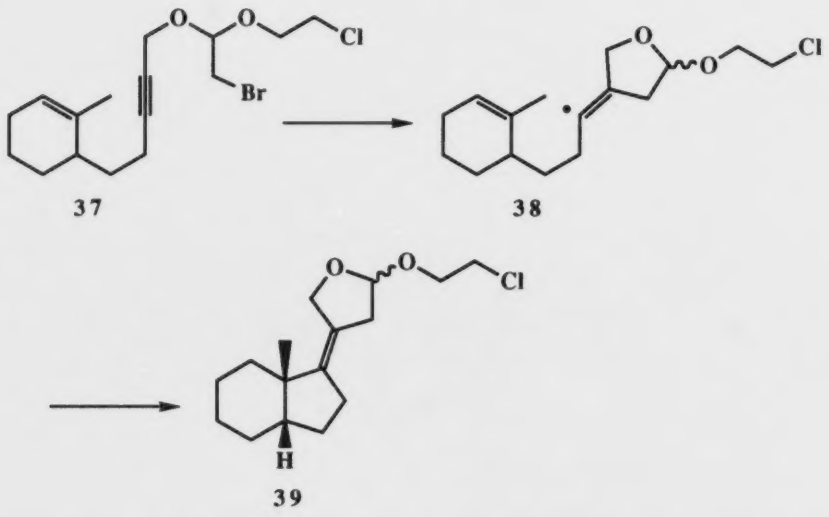
Two other methods exist for the generation of vinyl radicals. The procedures involve the intra- and intermolecular addition of radicals to alkynes.

Intramolecular Additions to Alkynes

The cyclization of an alkyl radical onto a triple bond results in formation of a new vinyl radical. The strong

preference for 5-*exo* digonal closure provides a route for the regiospecific formation of a vinyl radical (Scheme **13**).[26] The vinyl radical can then cyclize onto a suitably located multiple bond. Stork has used this approach in the preparation of the bicyclic compound **39**. 5-*Exo*

Scheme 13



37 38 39

cyclization of the radical generated from the bromide **37** gave vinyl radical **38**, which further cyclized to the *cis*-fused hydrindane **39**.

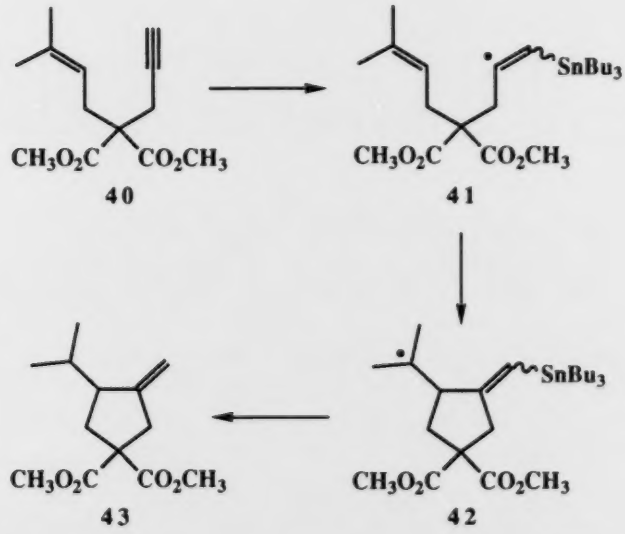
Intermolecular Additions to Alkynes

The intermolecular addition of a free radical onto a triple bond initially appeared as an unlikely candidate for the generation of a vinyl radical that would then undergo intermolecular cycloaddition to another olefin. This view

was based on the fact that the first radical addition would not only have to be selective for the triple bond but would also have to add regioselectively to that bond.[27] However, recent developments from the laboratories of Stork,[28] Oshima,[29] and Julia[30] have described an attractive route resulting from the direct intermolecular addition of a radical selectively to the triple bond of a suitable enyne. The following is a brief account of their exploratory experiments, followed by a survey of applications to the synthesis of hetero- and carbocycles.

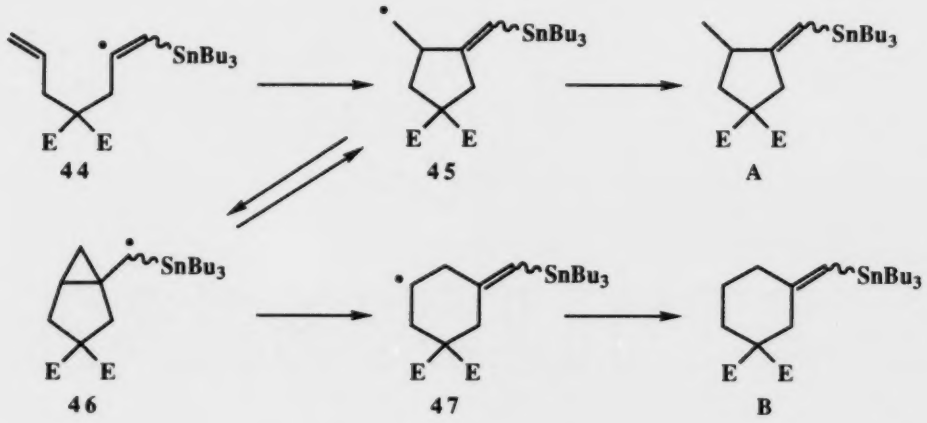
Treatment of enyne **40** with tributyltin hydride and AIBN in refluxing benzene gave the tin substituted methylenecyclopentane **43** in 85% yield.[28] The product was

Scheme 14



readily destannylated simply by stirring the material with dry silica gel in dichloromethane. It has been shown that methylenecyclohexanes are also produced during the reaction and the ratio of methylenecyclopentane to methylenecyclohexane depends on the concentration of the hydrogen donor, tributyltin hydride.[28a] At a concentration of 0.02 M tributyltin hydride, cyclization leads (Scheme **15**) to a 4:1 ratio of **A** to **B**. However, at much higher tin hydride concentrations (2.2 M) the exclusive product is the

Scheme 15

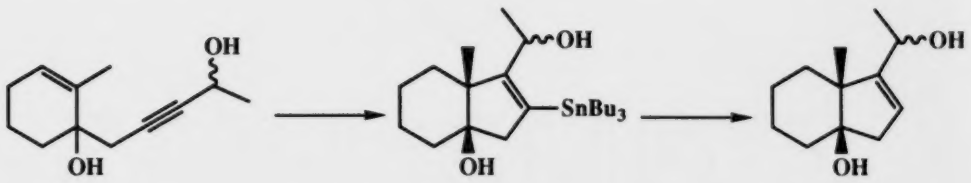


methylenecyclopentane **A**. These observations were explained based on the well precedented rearrangement of homoallylic radicals **45** via cyclopropylcarbinyl radicals **46**.[22e] In Scheme **15**, the initially formed vinyl radical (**44**) reacts by 5-*exo* cyclization. Under conditions of high stannane concentration (2.2 M) radical **45** is trapped to give the

methylenecyclopentane **A**. However, when the stannane concentration is lower, the initially cyclized radical can rearrange to give eventually the thermodynamically more stable methlenecyclohexane **B**.

The regiochemistry of the addition of trialkyl- or triaryltin radicals to terminal acetylenes is easily predicted but the situation with internal alkynes is not as straightforward. The cyclization of the acetylenic olefin **48** (Scheme **16**) demonstrates the potential scope of these reactions.[28b] Treatment of the unsymmetrical acetylenic diol **48** with tributyltin hydride gave the bicyclic compound **49**, which led to the indene **50** after destannylation.

Scheme 16

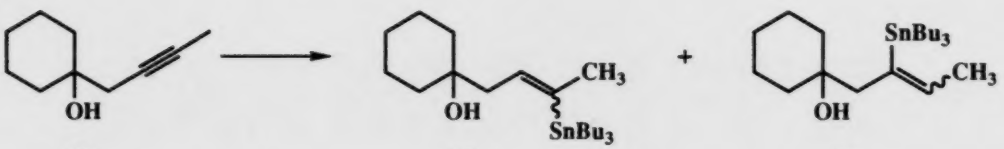


48 **49** **50**

Two important considerations arise from these results. First, they appear to imply preference of the stannyl radical for a triple rather than a double bond and, secondly, there appears to be a preference of the stannyl radical for that end of the triple bond which leads to **49**. Stork has shown that these results are, in fact, the consequence of reversibility of the addition of stannyl radicals not only to

double bonds but to triple bonds as well. Stannane addition to a double bond is actually faster than to a triple bond, but the reverse process is also faster for the double bond. Cyclization of the vinyl radical (from stannane addition to the triple bond) is faster than cyclization of the alkyl radical (from stannane addition to the double bond). Therefore cyclization occurs via the acetylene-stannyl radical adduct rather than via the corresponding olefin one. This was proven by the following experiment (Scheme **17**). Treatment of the alkyne **51** with tin hydride (0.02 M) in benzene and AIBN led to recovered starting material. Increasing the tin hydride concentration (0.77 M) resulted in a nearly equimolar mixture of the regioisomers **52** and **53**.

Scheme 17

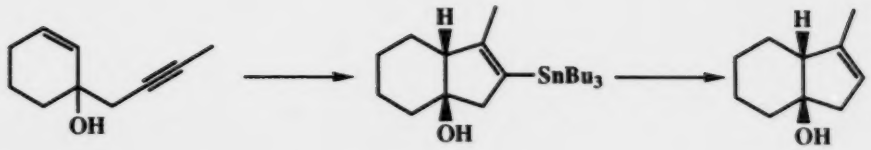


51 **52** **53**

However, treatment of the unsaturated analogue **54** under (0.02 M) concentration of tin hydride (Scheme **18**) led to the cyclized product **56** in 76% yield, after destannylation.

The addition of the tributyl tin radical to the alkyne must be rapid and reversible. At 0.02 M the concentration of tin hydride is not sufficiently high to intercept the intermediate vinyl radicals prior to fragmentation to alkyne

Scheme 18

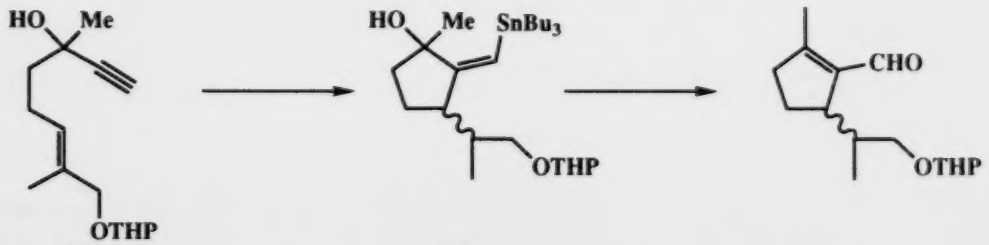


54 55 56

and tributyltin radical. However, if a (rapid) 5-exo cyclization pathway is available the vinyl radical can be intercepted. Addition of the tin radical to the other end of the triple bond produces a vinyl radical that does not cyclize rapidly and instead reverts to the starting alkyne. Eventually all of the starting alkyne is funnelled through to the cyclized product.

Oshima has described a similar procedure which resulted from his work on the triethylboron initiated hydrostannylation of alkynes.[29] Treatment of enyne **57** with triphenyltin hydride and a catalytic amount of triethylborane gave the vinyl stannane **58** in 84% yield. Collins oxidation

Scheme 19

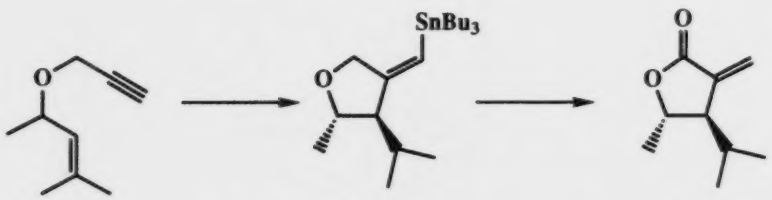


57 58 59

then produced the unsaturated aldehyde **59**. This method for generation of trialkyl- or triaryltin radicals has the particular advantage that the radical reaction may be performed at much lower temperatures (room temperatures or below) than reactions initiated thermally with azobisisobutyronitrile (AIBN).

Oshima has also described a preparation of α-methylene-γ-butyrolactones **62** via a triethylborane initiated cyclization of enynes of type **60**.[29c] Destannylation of the

Scheme 20

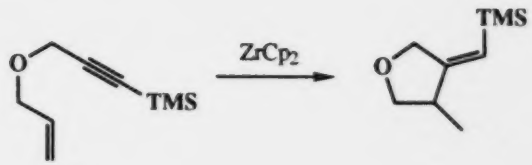


60 **61** **62**

vinyl stannane **61**, followed by oxidation, afforded efficient access to α-methylene-γ-butyrolactones, which represent a major class of known natural products and possess wide-ranging biological activities.[31]

The cyclizations of enynes described here may be compared with Negishi's complementary procedure.[32] Treatment of the silyl substituted enyne **63** with dicyclopentadienyl-zirconium gave **64** (compare Schemes **20** and **21**).

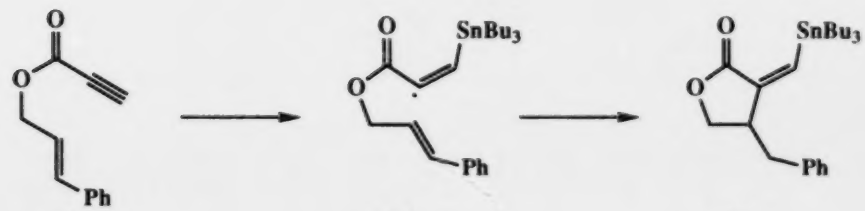
Scheme 21



63 64

Lee has also reported a new route to α-methylene-γ-butyrolactones based (Scheme **22**) on the radical cyclization of allylic propiolates.[33a] The Michael addition of triphenyltin radicals to the alkynoate **65** generated the vinyl radical **66** which then cyclized in a 5-*exo* fashion onto the

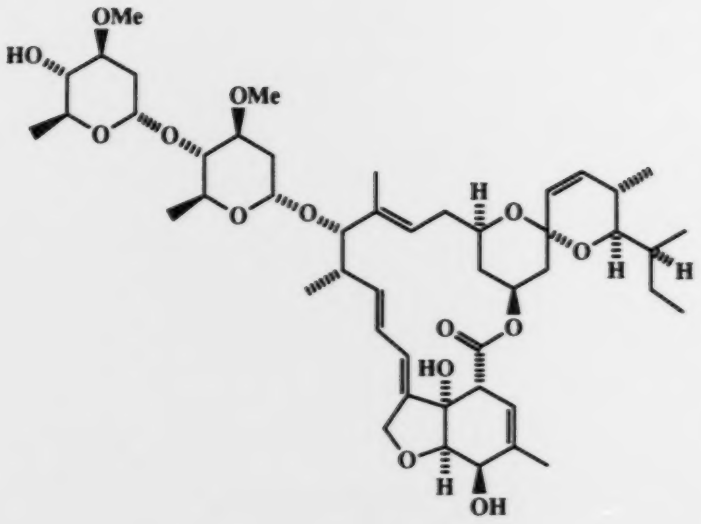
Scheme 22



65 66 67

allylic double bond. The work has been extended to the synthesis of the analogous α-methylene-γ-valerolactones.[33b]

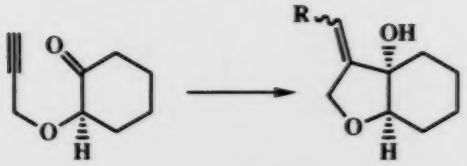
Julia has reported some model studies related to the southern moiety of the avermectins **68**.[30] Reductive cyclization of the acetylenic ketone **69** with sodium naphthalide failed; however, treatment with tributyltin hydride and AIBN gave a 50% combined yield of the



68 Avermectin B_{1a}

destannylated olefin **70a** and the stannyl adduct **70b** (Scheme **23**). Similar yields were obtained (Scheme **24**) with the β-keto ester **71**. Reaction of the corresponding silyl enol ether **73** under identical conditions gave better yields

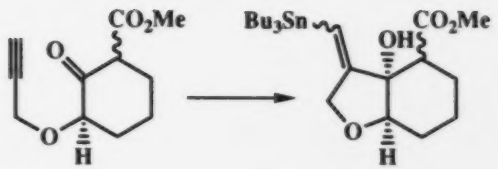
Scheme 23



69

70a R = H
70b R = $SnBu_3$

Scheme 24

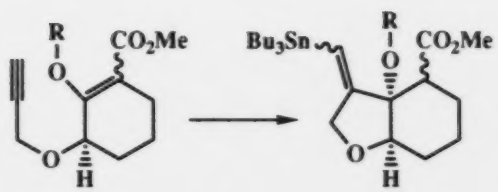


71 72

(50-60%) of the tertiary silyl ether **74** (Scheme **25**).

Julia suggests that the cyclization proceeds first by addition of the tin radical to the triple bond followed by further reaction of the generated vinyl radical with the

Scheme 25

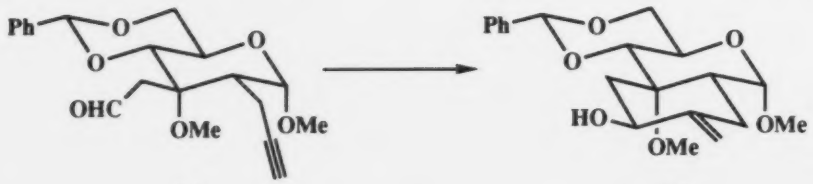


73 74

R = TMS

double bond of the enol ether or silyl enol ether. Enolization is not necessary because Fraser-Reid has shown, in his work in the carbohydrate field, that carbonyl groups act as efficient radical acceptors.[5] For example, treatment of the ynal **75** with tributyltin hydride gave the equatorial alcohol **76**, resulting from addition of the vinyl radical to the carbonyl of the aldehyde group (Scheme **26**).

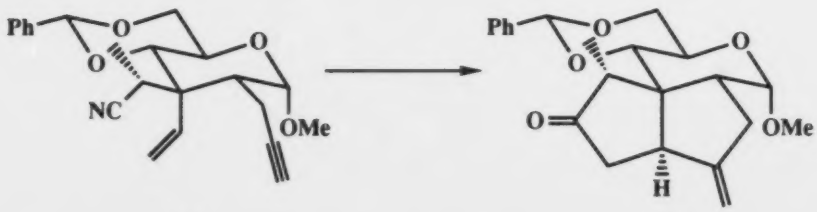
Scheme 26



75 **76**

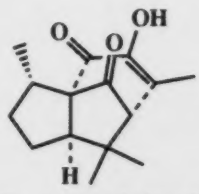
Fraser-Reid has also used vinyl radicals, resulting from the addition of stannyl radicals to terminal alkynes, in serial cyclizations (Scheme **27**).[34a] The resulting diquinane

Scheme 27



77 **78**

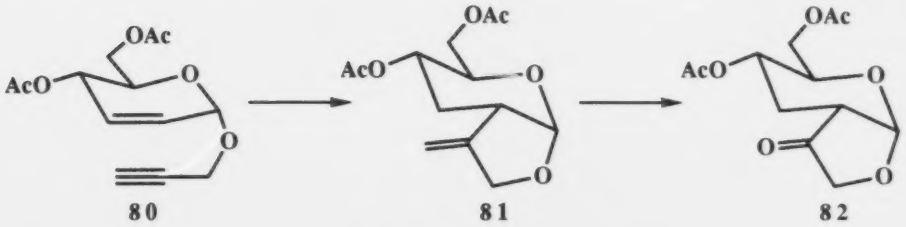
moiety served as the foundation in the first total synthesis of (-)-α-pipitzol **79** in optically pure form.[34b]



79 (-)-α-pipitzol

Chapleur has applied enyne radical closures to the stereocontrolled acylation of the C-2 or C-3 positions of unsaturated carbohydrates.[35] Radical cyclization of the propargyl acetal **80** afforded the olefin **81**, which was oxidatively cleaved with osmium tetroxide and sodium periodate. The two-step sequence allows stereocontrolled acylation of the carbohydrate at the C-2 position.

Scheme 28



80 **81** **82**

Nishida[36] has reexamined the cyclization of **69** and found that at a higher concentration of AIBN, the reaction was quite facile and the yield of **70** was essentially quantitative. This work has been extended to a novel synthesis of fused cycloheptanones and cyclooctenones from

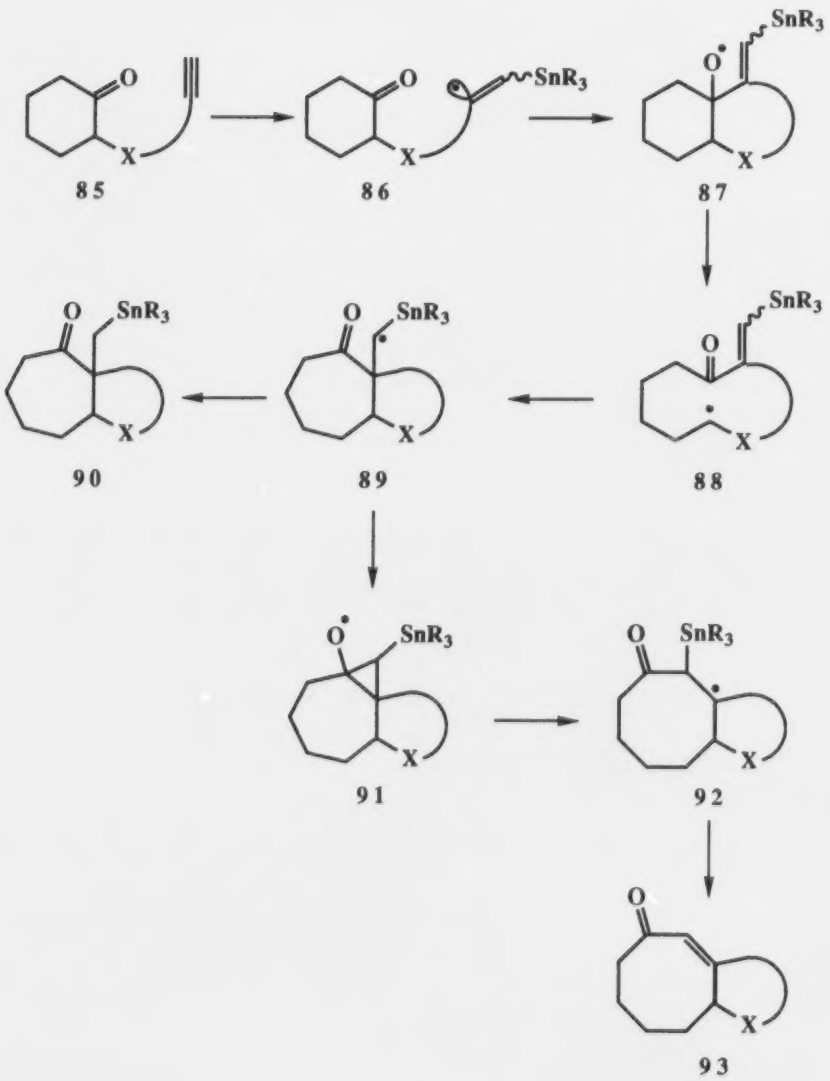
Scheme 29

83 **84**

cyclohexanones by combining the vinyl radical cyclization with subsequent alkoxy radical fragmentation and recyclization processes.

Irradiation of a toluene solution of the acetylenic

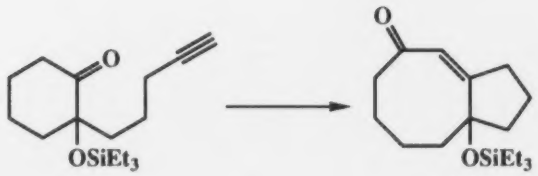
Scheme 30



ketone **83**, tributyltin hydride (1.2-1.4 equivalents) and AIBN (1.0 equivalent) with a 300W high-pressure mercury lamp produced the organostannane **84** in 62% yield (Scheme **29**).

The alkoxy radical **87** (Scheme **30**), resulting from addition of the vinyl radical to the ketone, undergoes β-cleavage[37] of the C-C bond to give the carbon radical **88**. Recyclization of the radical onto the vinyl stannane in a 5-*exo* fashion provides the radical **89** which is then reduced by tributyltin hydride. Application of this reaction to compound **94** (Scheme **31**), by slowly adding tributyltin hydride and AIBN to a solution of **94**, gave the cyclooctene **95** in 51% yield. This compound arises by the known cyclization of the

Scheme 31



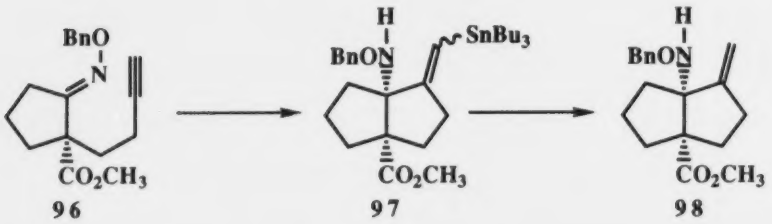
94 **95**

alkyl radical **89** onto the ketone (Scheme **30**), followed by further fragmentation and elimination (**91**→**93**).[38] Partitioning of the products between cycloheptanones **90** and cyclooctenones **93** is governed by the relative rates for the cyclization (**89**→**91**) and the reduction (**89**→**90**). If the

concentration of tributyltin hydride is sufficiently low, formation of cyclooctenone **93** will be favored.

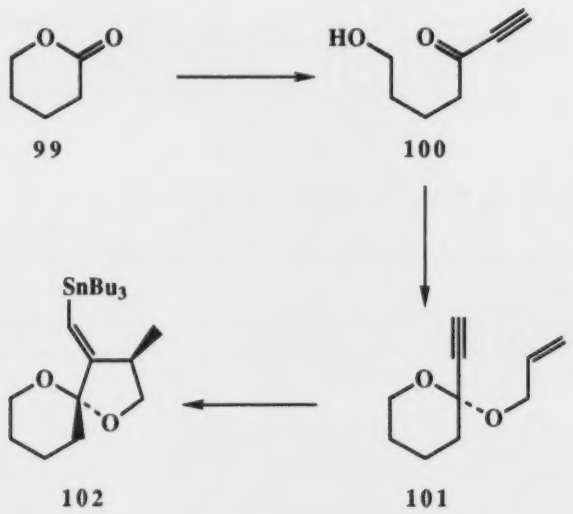
Oxime ethers can also be used as radical acceptors in vinyl radical cyclizations, as shown in the work of Enholm.[39]

Scheme 32



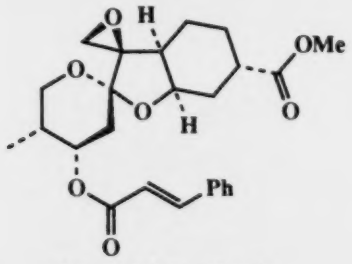
The bicyclic diquinane **98** was obtained in 90% yield from cyclization of the terminal alkyne **96** (Scheme **32**).

Scheme 33



Parsons has described an attractive method for preparation of spiroacetals, which relies on a tributyltin hydride mediated vinyl radical cyclization.[40] Cyclization of the enyne **101**, which was readily prepared in two steps from the lactone **99**, gave the spiroacetal **102** in 85% yield.

This reaction has been applied to a model study for construction of phyllanthocin **103**. Reaction of the keto



103 phyllanthocin

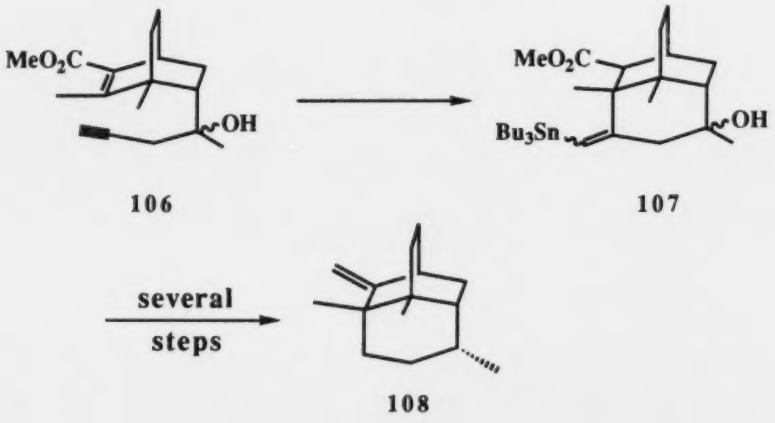
alcohol **100** with cyclohexenol gave the acetal **104**. Enyne cyclization with tributyltin hydride and AIBN, followed by destannylation with *n*-butyllithium, provided the spiroacetal **105**. This sequence represents a straightforward entry into the phyllanthocin ring system.

Scheme 34

104 **105**

Rao[41] has reported a total synthesis of racemic seychellene (**108**), which has, as a key step, a vinyl radical intramolecular Michael addition (Scheme **35**). Addition of tributyltin radical to the terminal acetylene of **106** and cyclization onto the β-position of the unsaturated ester gave the tricyclic hydroxy ester **107** in 75% yield. The ester was then converted in several steps into (±)-seychellene (**108**).

Scheme 35



106 **107** **108**

(±)-seychellene

Conclusions

It is obvious from the above discussion that enyne cyclizations are becoming increasingly popular. The examples serve to illustrate the attractive features of this method for the generation and cyclization of vinyl radicals. Alkynes are often readily available and the vinyl stannanes

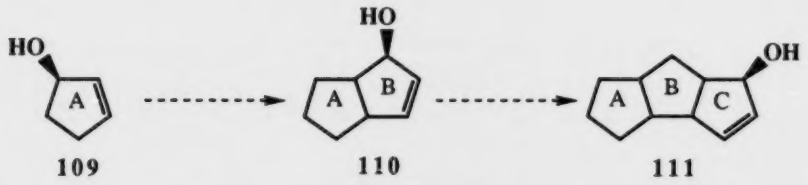
produced are usually formed with excellent stereoselectivity. The synthetic applications of the vinyl stannanes are well known.[42] They can be used as precursors of vinyl halides,[43] vinyl carbanions,[44] olefins (via protiodestannylations), or carbonyl compounds (via epoxidation).[45] They can also be used in coupling reactions.[46] Vinyl selenides[47] and vinyl sulfides[48] are available from related cyclizations of enynes, utilizing selenoboranes and thiophenol.

II. DISCUSSION

At the start of this project we set as our goal the development of an iterative procedure for annulating five membered rings onto existing cyclic structures, and we were particularly interested in making use of the attractive features of free radical reactions. The incentive for this work was the abundance of structurally interesting polyquinane natural products.[49]

In order to make the cyclopentannulation iterative, we required the ring-forming process to finish with suitable functionality on the new five-membered ring such that the whole sequence could be repeated directly or after some straightforward manipulations. The type of functionality we chose was the allylic alcohol unit and Scheme **36** outlines the procedure we wished to develop.

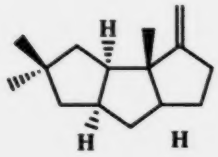
Scheme 36



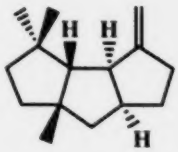
109 **110** **111**

Starting with a cyclic allylic alcohol **109** (ring A), we wished to attach a new ring (B) which retained allylic alcohol functionality (as in **110**). After another iteration

we would obtain the tricyclic structure **111** which represents the carbon framework of such natural triquinanes as hirsutene **112**[50] and capnellene **113**.[51]



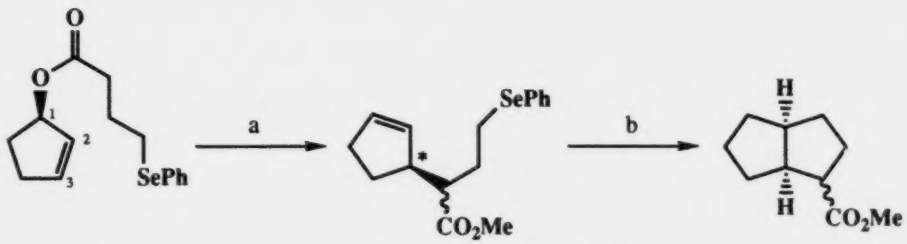
112 hirsutene



113 capnellene

Previous work[52] from this laboratory indicated the potential of a process for making five membered carbocycles from allylic alcohols using a sequence that involves Ireland

Scheme 37



114 **115** **116**

Scheme 37. Reagents and conditions: (a) LDA, TMSCl, then CH_2N_2; (b) Ph_3SnH, AIBN.

ester enolate rearrangement and radical cyclization (Scheme **37**).

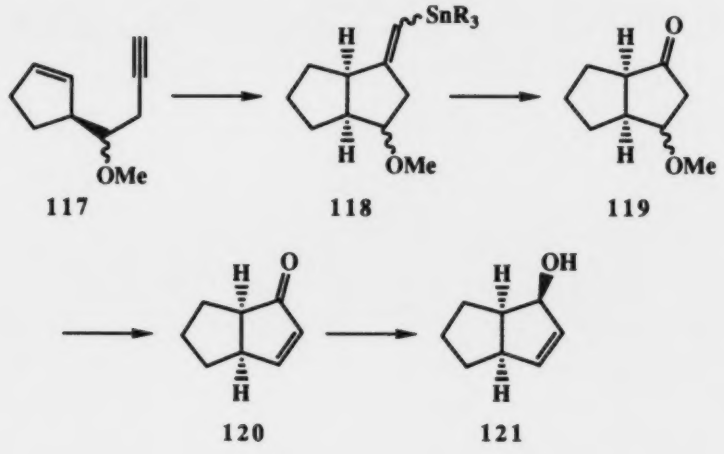
In the first step of this sequence the alcohol is acylated with 4-(phenylseleno)butyroyl chloride. The subsequent Claisen rearrangement serves two important

functions. The suprafacial nature of the rearrangement means that the stereochemistry of the esters (see **115**, starred atom) is controllable by proper choice of stereochemistry at C-1 of the allylic alcohol. The rearrangement also moves the double bond into a suitable position to capture the radical generated from the selenide. A limitation of this methodology is the loss of functionality on the carbocycle that is formed.

As indicated in the introduction, vinyl radical cyclizations have the chemically valuable feature that the resulting product has a double bond in a predetermined position, and we sought to use this characteristic so as to introduce functionality on the newly annulated ring.

In our initial approach we evaluated a sequence that included an Ireland ester enolate rearrangement followed by vinyl radical cyclization (Scheme **38**). The target molecule of this sequence was the enyne **117**, which we planned to use

Scheme 38

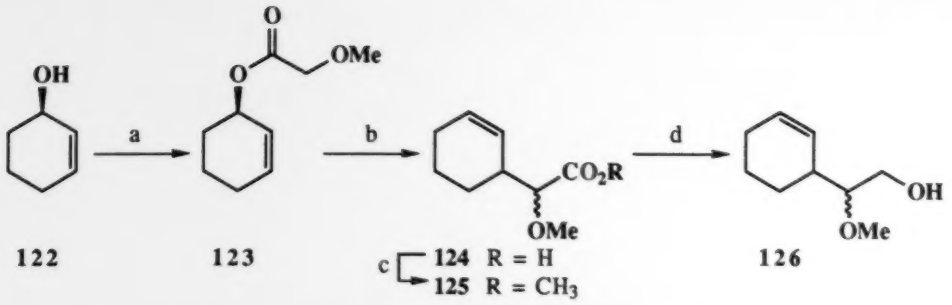


in a stannane mediated vinyl radical cyclization to afford **118**. Oxidative cleavage of the exocyclic double bond in **118** and base-induced elimination of the β-methoxy substituent would then give the enone **120**, and reduction of this material would generate **121**, which contains the desired allylic alcohol functionality.

According to our plan, **117** would be prepared by ester enolate rearrangement (Scheme **39**)of the *O*-protected allylic glycolate ester **123**, itself available by acylation of 2-cyclohexen-1-ol with the acid chloride of 2-methoxyacetic acid.[53] For our initial investigations we chose 2-cyclohexen-1-ol because it was readily obtained from the $CeCl_3$-$NaBH_4$[54] reduction of commercially available 2-cyclohexen-1-one. The α-substituted acetate was used as it would allow facile introduction of a double bond at a later stage. The acetate was prepared in 85% yield, and rearrangement under standard conditions gave the acid **124**, which was immediately esterified with diazomethane. The ester was then reduced to alcohol **126**, using an excess of DIBAH in dichloromethane. The intermediate aldehyde can be isolated if the reaction is quenched at low temperature (-78°C), but, if the reaction mixture is allowed to warm to room temperature complete reduction to the alcohol occurs.

At this point we searched for a more efficient synthesis of compounds of type **126**, and we were pleased to find that an

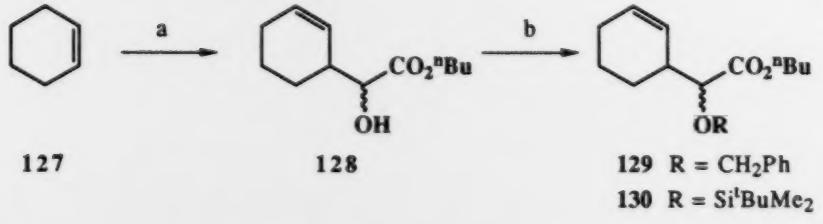
Scheme 39



Scheme 39. Reagents and conditions: (a) $MeOCH_2COCl$, pyridine; (b) LDA, TMSCl; (c) CH_2N_2; (d) DIBAH.

ene reaction[55] afforded alcohol **128** in one step from cyclohexene (Scheme **40**). Addition of tin tetrachloride to a solution of cyclohexene and *n*-butyl glyoxal[56] in dichloromethane at -78°C gave the hydroxy ester **128** in 82% yield. This route was attractive not only because of its efficiency but also because the free hydroxyl would allow us to investigate the effect of different OR groups on the elimination step that comes later in the sequence. In this

Scheme 40

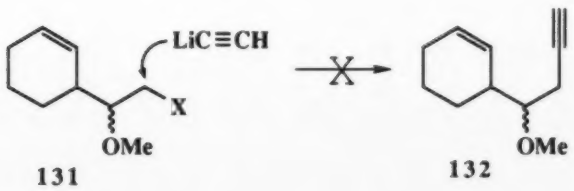


Scheme 40. Reagents and conditions: (a) $^{n}BuO_2CCHO$, $SnCl_4$; (b) NaH, BnBr or NaH, $^{t}BuMe_2SiCl$.

regard the hydroxyl was protected as its benzyl **129** and silyl **130** ethers.

All that was now required to prepare enyne **117** was to displace a derivative of alcohol **126** with lithium acetylide (Scheme **41**). The tosylate and the corresponding bromide were prepared; however they proved to be inert to displacement by acetylide under a variety of conditions, even though a number of examples exist in the literature for displacement of primary halides and tosylates with the anions of acetylene and substituted acetylenes.[57] We tried changing a number of

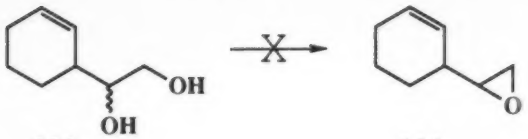
Scheme 41



conditions including solvent and temperature, and the effect of various additives. However, the results were unpromising. It appears that displacement of α-alkoxy substituted halides and tosylates (or mesylates) is generally difficult. Such a problem has been observed before in this laboratory during the total synthesis of mevinolin.[58]

We briefly investigated the preparation (Scheme **42**) of epoxide **134** from diol **133**,[59a] because the addition of aluminum acetylides to epoxides is known[59b] to be a facile

Scheme 42



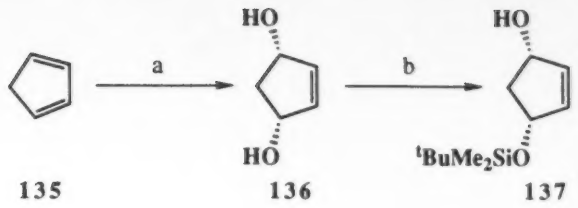
133 **134**

process. However, this was also an unsatisfactory alterative because epoxide **134** is rather volatile and its isolation troublesome.

It was clear that a different approach would have to be used. Our initial sequence failed because we were unable to introduce the acetylene (as in Scheme **41**). We felt that the problem was due to the α-alkoxy substituent, which we had incorporated in order to facilitate introduction of a double bond later in the process. It occurred to us that the alkoxy group might not be necessary because a number of literature methods[60] exist for desaturating ketones in the α,β position, and we could use one of these methods at the appropriate stage.

To implement these ideas we chose the allylic alcohol **137**[61] as our starting material. Incorporation of the *tert*-butylsilyloxy substituent was done simply to avoid problems due to volatility. Alcohol **137** was easily made in two steps from cyclopentadiene, as shown in Scheme **43**,[62] and mono-

Scheme 43

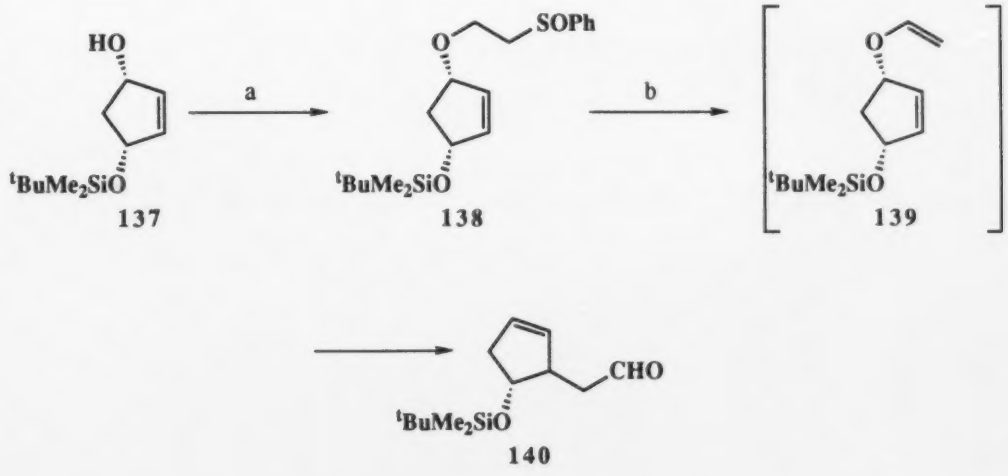


Scheme 43. Reagents and conditions: (a) O_2, *hv*, rose bengal; (b) NaH, ^{t}BuMe$_2$SiCl

protection of diol **136** was achieved using the procedure described by McDougal.[63]

The vinyl ether of alcohol **137** was now required as the substrate for the Claisen rearrangement. The standard method for preparing vinyl ethers of allylic alcohols is by vinyl

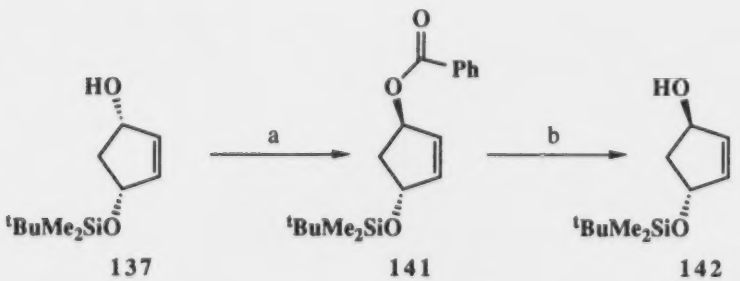
Scheme 44



Scheme 44. Reagents and conditions: (a) NaH, CH_2=CHSOPh; (b) Δ.

ether exchange catalyzed by mercuric(II) salts;[64] however, a mercury free process[65] utilizing aryl vinyl sulfoxides was initially attempted (Scheme **44**). The sodium salt of alcohol **137** was added in a Michael fashion to phenyl vinyl sulfoxide. The 2-allyloxyethyl phenyl sulfoxide **138** was obtained in good yield, but thermal elimination and rearrangement was not successful and decomposition occurred. Not knowing whether the problem originated in the elimination of PhSOH from **138** or at the stage of the Claisen rearrangement, we prepared the vinyl ether **139** using the standard mercury-catalyzed procedure. However, attempted thermal rearrangement of vinyl ether **139** also resulted in complete decomposition of the starting material. On examination of Dreiding models we felt that the problem may have been steric in nature and that the bulky protecting group might prevent proper orientation of the vinyl unit for Claisen rearrangement. [Subsequent results (see later) suggest that it should indeed be possible

Scheme 45

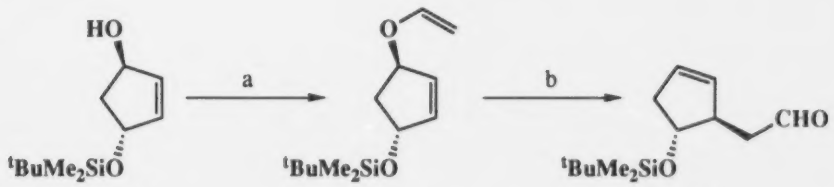


137 **141** **142**

Scheme 45. Reagents and conditions: (a) DEAD, Ph_3P, $PhCO_2H$; (b) LAH.

to effect the Claisen rearrangement using conditions that we subsequently used.] At this point, therefore, the configuration of the alcohol was inverted using the Mitsunobu procedure (Scheme **45**).[66] Again the vinyl ether was prepared using mercuric acetate and ethyl vinyl ether. The experimental conditions were quite critical, and, in order to obtain reproducible yields a full equivalent of mercuric acetate was used in this and subsequent transetherifications. The vinyl ether **143** underwent smooth rearrangement (Scheme **46**) upon heating at 200°C in decalin for 15 minutes. The

Scheme 46



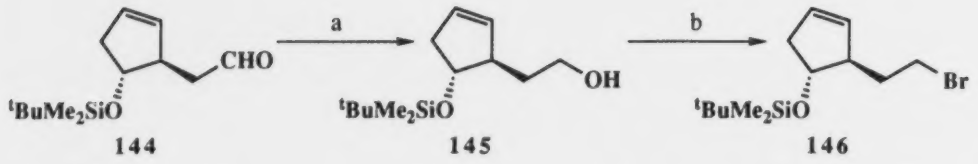
142 **143** **144**

Scheme 46. Reagents and conditions: (a) $Hg(OAc)_2$, $EtOCH=CH_2$; (b) Δ

resulting aldehyde **144** was reduced, and the alcohol **145** converted (Scheme **47**) into the corresponding bromide **146** with triphenylphosphine and carbon tetrabromide.

After our experiences with compound **131** we were pleased to find that the bromide **146** underwent smooth displacement with lithium acetylide. We were now ready to close the ring via vinyl radical cyclization. Although this reaction can be

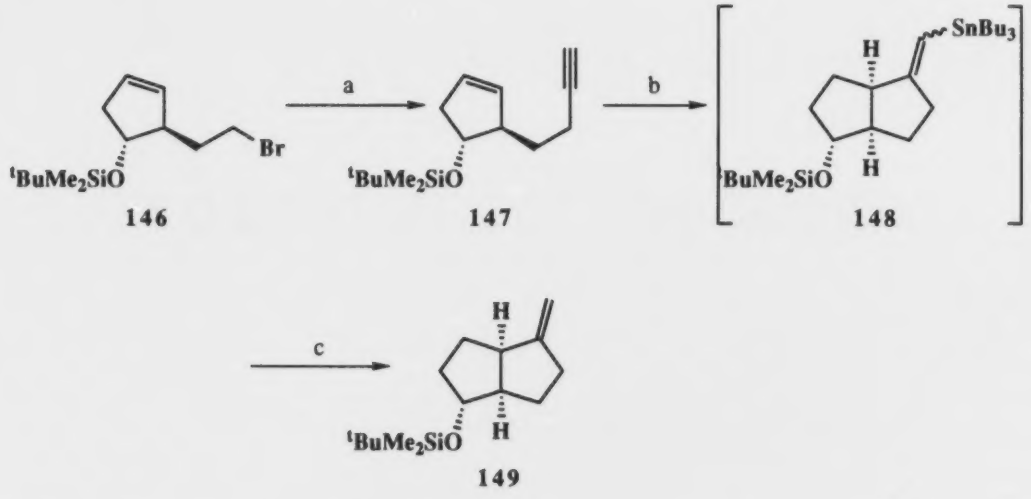
Scheme 47



Scheme 47. Reagents and conditions: (a) LAH; (b) Ph_3P, CBr_4.

carried out under a variety of conditions, the procedure developed by Oshima[29] was adopted because of its simplicity. Treatment of a hexane solution of enyne **147** (0.02 M) and tributyltin hydride with triethylborane at room temperature resulted in cyclization to the vinyl stannane **148** (Scheme **48**). Protiodestannylation occurred upon flash chromatography

Scheme 48

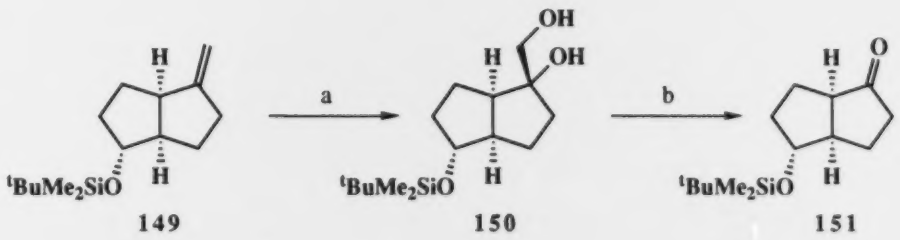


Scheme 48. Reagents and conditions: (a) LiCCH, HMPA; (b) ^{n}Bu$_3$SnH, Et_3B, O_2; (c) SiO_2, H_2O.

and compound **149** was isolated in 76% yield from the enyne **147**.[28b]

The exocyclic double bond was then cleaved (Scheme **49**) using a two-step procedure which involved dihydroxylation with osmium tetroxide[67] followed by glycol cleavage with lead tetraacetate.[68] Cleavage was attempted in one step by the Lemieux-Johnson procedure;[69] however better yields were obtained if the diol was isolated.

Scheme 49

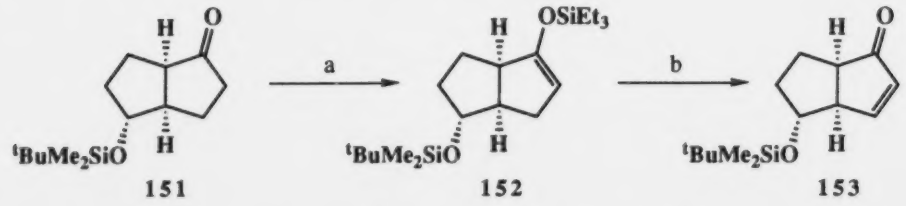


Scheme 49. Reagents and conditions: (a) OsO_4, 4-methylmorpholine-N-oxide; (b) $Pb(OAc)_4$.

A number of procedures exist for introducing a double bond α to a ketone.[60] Initially we attempted to use selenium chemistry[60a-c] for this purpose, but the selenenylation of the kinetic enolate of **151** with benzeneselenenyl chloride proved to be troublesome. Monoselenenylation of the ketone was accompanied by formation of bis-selenenylated product, and unreacted starting material was always present. Attempted separation of the reaction products by flash chromatography resulted in considerable loss due to the instability of the

selenenyl ketone. Oxidation of the silyl enol ether (Scheme **50**) of ketone **151** with palladium(II)acetate[60d,e] was next examined. A 42% yield of the desired enone **153** was obtained; however, prolonged reaction times and large excesses of the palladium catalyst were required.

Scheme 50



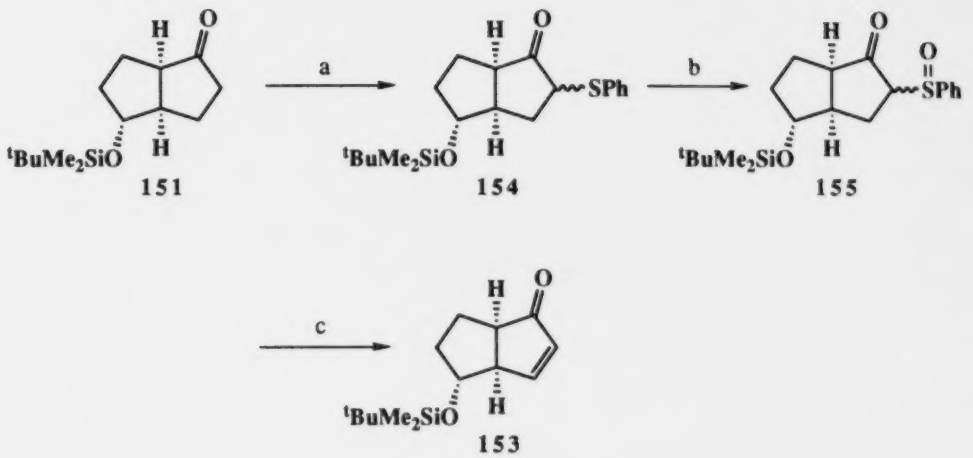
151 **152** **153**

Scheme 50. Reagents and conditions: (a) LDA, Et_3SiCl; (b) $Pd(OAc)_2$

An acceptable yield of enone **153** was finally obtained using Trost's sulfenylation-dehydrosulfenylation sequence.[60f] The α-sulfenyl ketone **154** was oxidized with MCPBA and the resulting sulfoxide eliminated in refluxing toluene (Scheme **51**). The sulfenylation reaction seems less prone to bis-sulfenylation and the α-sulfenyl ketones produced appear to be more stable than the corresponding α-selenenyl counterparts.

1,2-Reduction (Scheme **52**) of the enone **153** was carried out using $CeCl_3$ and $NaBH_4$.[54] As expected, a single alcohol was obtained resulting from addition of hydride to the less

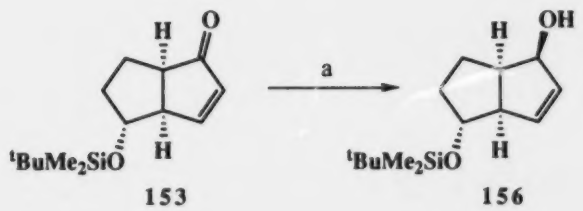
Scheme 51



Scheme 51. Reagents and conditions: (a) LDA, $(PhS)_2$; (b) MCPBA; (c) Δ.

hindered (convex) face of the diquinane **153**.

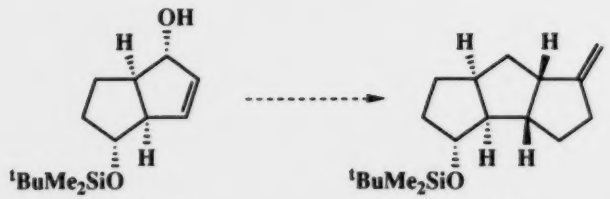
Scheme 52



Scheme 52. Reagents and conditions: (a) $CeCl_3$, $NaBH_4$.

Formation of the allylic alcohol **156** represents completion of the first iteration of the cyclopentannulation sequence. Two possible routes were available to us: (a) If the stereochemistry of the allylic alcohol were inverted and the cyclopentannulation sequence repeated (Scheme **53**) then the triquinane **158** would be obtained, which has the linearly

Scheme 53



157 **158**

fused *cis,anti,cis*-tricyclo-[6.3.0.0.^{2,6}]undecane carbon skeleton common to many of the tricyclopentanoid natural products. (b) If, however, the cyclopentannulation sequence is repeated on alcohol **156** (Scheme **54**) then triquinane **159** would be now be formed. This possesses the unnatural *cis,syn,cis*-tricyclo-[6.3.0.0^{2,6}]undecane carbon skeleton.

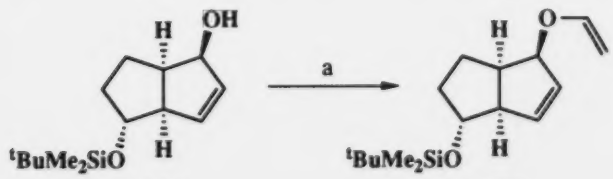
Scheme 54

156 **159**

We felt that this later route would be more difficult owing to the more hindered nature of alcohol **156**, in which the hydroxyl group resides in the pocket formed by the cis fused diquinane. The conversion **156→159** was chosen because we wished to examine the more demanding sequence.

Alcohol **156** proved to be very hindered indeed and vinylation with mercuric acetate and ethyl vinyl ether suffered from low conversion. Upon prolonged heating under the reaction conditions, alcohol **156** decomposed to an appreciable extent. It was thought that the silyl protecting group might be removed under the slightly acidic conditions of the vinylation. Potassium carbonate was added to the mixture in an attempt to prevent this side reaction; however, the base inhibited the vinylation. Some improvement was obtained when the reaction mixture was buffered with sodium acetate.[64] These conditions allowed prolonged reaction times and a 72% yield of the vinyl ether **160** was obtained (Scheme **55**). Although the product was contaminated with a small amount of impurities, the material was used directly in the next experiment without any purification, except for filtration through a pad of silica gel to remove mercuric salts.

Scheme 55



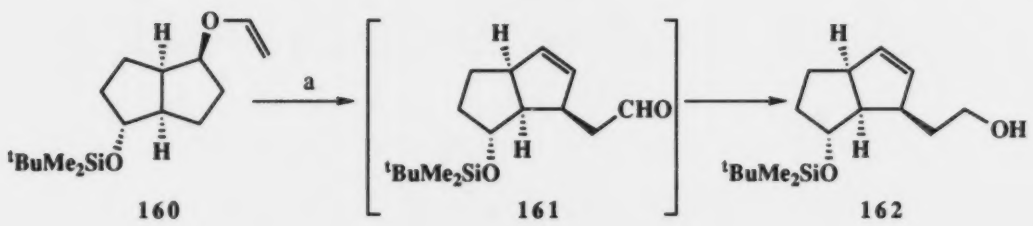
156 **160**

Scheme 55. Reagents and conditions: (a) $Hg(OAc)_2$, $EtOCH{=}CH_2$, NaOAc.

The Claisen rearrangement of vinyl ether **160** was expected to be troublesome after the problems experienced in its preparation. Extensive decomposition occurred upon heating in refluxing decalin. A search of the literature revealed that Claisen rearrangements are catalyzed by organoaluminum compounds.[70] Treatment of a cooled (-78°C) solution of the vinyl ether in dichloromethane with an excess of triisobutylaluminum (TRIBAL) yielded alcohol **162** in 95% yield. TRIBAL not only catalyzed sigmatropic rearrangement but also reduced the intermediate aldehyde (via a Meerwein-Ponndorf-Verley reduction) to alcohol **162**.

Diisobutylaluminum hydride

Scheme 56

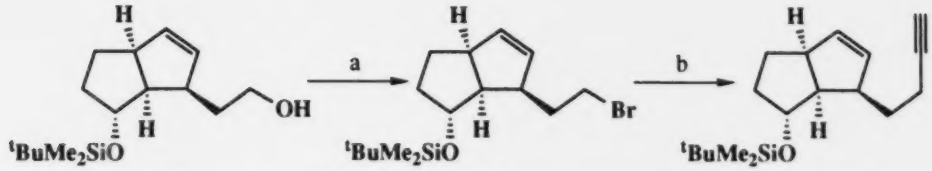


Scheme 56. Reagents and conditions: (a) ^{i}Bu$_3$Al.

was not as effective, and a mixture of alcohol **162** and allylic alcohol **156** was obtained.[71]

Bromide **163** was prepared and the halogen displaced with lithium acetylide to give enyne **164** in 85% overall yield from vinyl ether **160**.

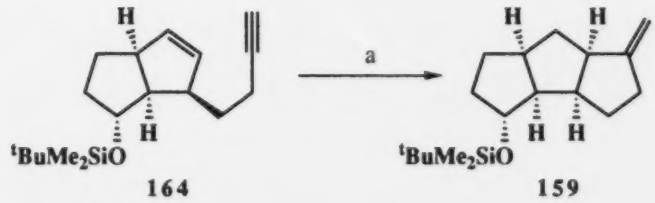
Scheme 57



Scheme 57. Reagents and conditions: (a) Ph_3P, CBr_4; (b) LiCCH, HMPA.

Enyne **164** proved to be inert to the conditions used previously for the cyclization of **147**, but when the reaction was initiated with AIBN in refluxing *toluene* the triquinane **159** was isolated in 79% yield after destannylation.

Scheme 58



Scheme 58. Reagents and conditions: (a) ^{n}Bu$_3$SnH, AIBN, Δ.

Conclusions

We have developed a cyclopentannulation procedure using a Claisen rearrangement-vinyl cyclization sequence. The suprafacial nature of the Claisen rearrangement and cis ring fusion stereochemistry of the 5-*exo* cyclization allow complete stereocontrol in the annulation sequence. Synthetic applications of the procedure are currently being studied in this laboratory.

III. EXPERIMENTAL

General

Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120°C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use. Petroleum ether refers to the fraction bp 35-60°C.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30°C using a rotary evaporator.

Temperatures recorded for kugelrohr distillations refer to air-bath temperatures and are not true boiling points. The values indicate the temperature at which the distilate begins to condense in the receiving flask.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid,[72] followed by charring on a

hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium and benzophenone ketyl. Dry benzene was distilled from sodium. Dry diisopropylamine, triethylamine, dichloromethane, methanol, pyridine, *N,N*-dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride, the last two solvents being distilled under water pump vacuum. Commercial (Aldrich) solutions of *n*-butyllithium (in hexanes) and methyllithium (in ether) were assumed to have the stated molarity.

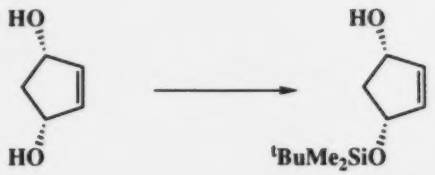
Infrared spectra were recorded on a Nicolet 7000 FT-IR instrument. Measurements were made as casts from the specified solvent and using potassium bromide plates.

Proton nuclear magnetic resonance spectra were recorded with Bruker WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded with Bruker WP-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker AM-400 (at 100.6 MHz) spectrometers using deuterochloroform as an internal standard.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department.

***cis* 4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclopenten-1-ol (137).**

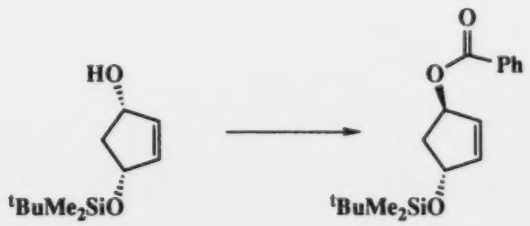


136 **137**

Sodium hydride (804.0 mg, 60%w/w in oil, 20.10 mmol) was washed with hexane (2 x 5 mL) and suspended in THF (30 mL). A solution of diol **136**[62] (2.0115 g, 20.10 mmol) in THF (10 mL plus 2 mL as a rinse) was added dropwise to the stirred suspension and vigorous stirring was continued for 1 h. *tert*-Butyldimethylsilyl chloride (3.0283 g, 20.10 mmol) in THF (5 mL plus 2 mL as a rinse) was added, and stirring was continued overnight. The mixture was poured into a solution of diethyl ether (200 mL) and methanol (50 mL), and the suspension was filtered through a pad (5 x 3 cm) of silica gel. The pad was washed with ethyl acetate (300 mL) and the filtrate was evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using first 20% ethyl acetate-hexane and then 1:1:3 methanol-ethyl acetate-hexane, gave unreacted diol **136** (205 mg, 10%) and silyl ether **137** (3.7053 g, 85%; 96% after correction for recovered starting material) as a pure [TLC, silica, 20% ethyl acetate-hexane], colorless

oil: FTIR (CH_2Cl_2 cast) 3340, 2956, 2930, 2886, 2857, 1472, 1463, 1366, 1252, 1128, 1099, 1072, 1021, 1006, 905, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.48 (ddd, J = 14.0, 4.5, 4.5 Hz, 1 H), 2.19 (br s, 1 H), 2.66 (ddd, 14.0, 7.0, 7.0 Hz, 1 H), 4.51-4.67 (m, 2 H), 5.82-5.93 (m, 2 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.62, 18.17, 25.92, 44.74, 75.18, 135.64, 136.97; exact mass *m/z* calcd for $C_7H_{13}O_2Si$ (M - *t*-Bu) 157.0685, found 157.0682. An analytical sample was prepared by Kugelrohr distillation (65°C, 0.075 mm Hg). Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.43; H, 10.42.

trans [4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclopenten-1-yl] benzoate (141).

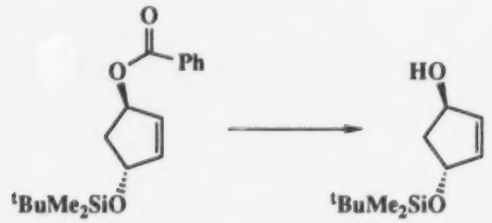


137 **141**

Triphenylphosphine (1.2724 g, 4.85 mmol) and benzoic acid (592.4 mg, 4.85 mmol) were added successively to a stirred solution of alcohol **137** (520 mg, 2.43 mmol) in THF (20 mL) at room temperature. Diethyl azodicarboxylate (0.76 mL, 4.85 mmol) in THF (4 mL) was then added dropwise (ca 5 min) and stirring was continued for 4 h. The solvent was evaporated and flash chromatography of the residue over

silica gel (4 x 15 cm), using 5% ethyl acetate-hexane, gave benzoate **141** (748.1 mg, 97%) as a pure [TLC, silica, 5% ethyl acetate-hexane], colorless oil: FTIR (CH_2Cl_2 cast) 2955, 2929, 2857, 1719, 1271, 1108, 1087, 1070, 1027, 903, 837, 776, 712 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 2.10-2.38 (m, 2 H), 5.07-5.16 (m, 1 H), 5.98-6.11 [m, 3 H (contains singlet at δ 6.08)], 7.35-7.58 (m, 3 H), 7.96-8.06 (m, 2 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.66, 18.19, 25.87, 41.16, 76.33, 76.41, 128.27, 129.55, 130.40, 131.46, 132.85, 141.05, 166.49; exact mass *m/z* calcd for $C_{18}H_{26}O_3Si$ 318.1651, found 318.1650. Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found: C, 68.13; H, 8.39.

***trans* 4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclopenten-1-ol (142).**

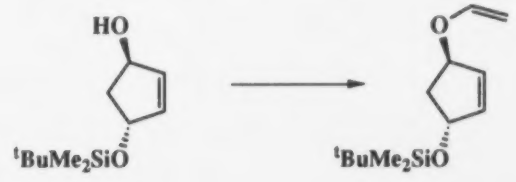


141 **142**

A solution of ester **141** (2.3262 g, 7.30 mmol) in THF (10 mL) was added dropwise at room temperature to a stirred suspension of lithium aluminum hydride (554.4 mg, 14.61 mmol) in THF (31 mL). Stirring was continued for 15 min and then the mixture was quenched by successive addition of water (0.6 mL), 15% aqueous sodium hydroxide (0.6 mL), and water (1.8

mL). The resulting mixture was stirred at room temperature for 20 min and filtered through a pad (5 x 3 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using first dichloromethane and then 10% ethyl acetate-dichloromethane, afforded alcohol **142** (1.4755 g, 94%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 3333, 2955, 2930, 2887, 2857, 1472, 1463, 1364, 1255, 1123, 1082, 1065, 1038, 1006, 958, 904, 864, 836, 796, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.05 (s, 6 H), 0.87 (s, 9 H), 1.80 (br s, 1 H), 1.97-2.04 (m, 2 H), 4.94-5.10 (m, 2 H), 5.88-5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.62, 18.22, 25.92, 44.54, 76.24, 76.41, 135.55, 136.36; exact mass *m/z* calcd for $C_{11}H_{22}O_2Si$ 214.1389, found 214.1388. An analytical sample was prepared by Kugelrohr distillation (111°C, 15 mm Hg). Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.61; H, 10.41.

Ethenyl *trans* [4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]cyclopent-2-en-1-yl] ether (143).



142 **143**

Mercuric acetate (462.7 mg, 6.42 mmol) was added at room temperature to a solution of alcohol **142** (1.3755 g, 6.42

mmol) in freshly distilled ethyl vinyl ether (70 mL), and the resulting solution was refluxed for 18 h. Anhydrous potassium carbonate (4.0 g) was added to the cooled mixture and the excess of ethyl vinyl ether was evaporated (water pump). The residue was taken up in dichloromethane (50 mL) and filtered through a pad (3 x 5 cm) of silica gel, using first dichloromethane and then ethyl acetate. The dichloromethane filtrate was evaporated to give vinyl ether **143** (1.2341 g, 80%, 99% after correction for recovered starting material) as a colorless oil containing trace impurities [^{1}H NMR]: FTIR (CH_2Cl_2 cast) 2955, 2930, 2857, 1640, 1611, 1370, 1254, 1192, 1178, 1124, 1072, 1040, 978, 904, 857, 836, 814, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.96 (ddd, J = 14.5, 7.0, 4.0 Hz, 1 H), 2.20 (ddd, J = 14.5, 7.0, 2.5 Hz, 1 H), 4.01 (dd, J = 6.5, 2.0 Hz, 1 H), 4.21 (dd, J = 14.0, 2.0 Hz, 1 H), 4.99-5.12 (m, 2 H), 5.95-6.04 (m, 2 H), 6.35 (dd, J = 14, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.64, 18.19, 25.91, 41.01, 76.45, 82.34, 88.16, 131.67, 140.22, 150.57; exact mass *m/z* calcd for $C_{13}H_{24}O_2Si$ 240.1545, found 240.1549. A satisfactory combustion analysis could not be obtained.

Evaporation of the ethyl acetate filtrate gave the starting alcohol **142** (263.3 mg, 19%).

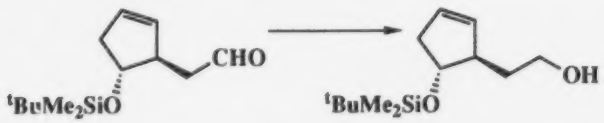
trans **5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-cyclopent-2-ene]acetaldehyde (144).**

143 **144**

A solution of vinyl ether **143** (1.1533 g, 4.80 mmol) in decalin (30 mL) was refluxed (bath temperature. 200°C) for 20 min. The mixture was cooled, diluted with hexane (50 mL), and filtered through a pad (5 x 3 cm) of silica gel. The pad was washed with hexane (100 mL) and the filtrate was discarded. The pad was then washed with ethyl acetate (200 mL) and the filtrate was evaporated. Flash chromatography of the residue over silica gel (4 x 14 cm), using 5% ethyl acetate-hexane, afforded aldehyde **144** (1.0415 g, 90%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2930, 2896, 2887, 2857, 1727, 1472, 1257, 1252, 1114, 1070, 880, 837, 776, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.04 (s, 6 H), 0.87 (s, 9 H), 2.16-2.64 (m, 4 H), 2.92-3.06 (m, 1 H), 4.05 (ddd, J = 7.0, 5.0, 5.0 Hz, 1 H), 5.56-5.71 (m, 2 H), 9.77 (t, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.77, -4.46, 18.00, 25.84, 41.38, 47.26, 48.83, 78.53, 129.19, 131.38, 201.64; exact mass m/z calcd for $C_9H_{15}O_2Si$ (M - t-Bu) 183.0841, found 183.0839. An analytical sample was prepared by Kugelrohr distillation (55°C, 0.005 mm Hg). Anal. Calcd

for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 65.07; H, 9.86.

***trans* [5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-cyclopent-2-ene]ethanol (145).**

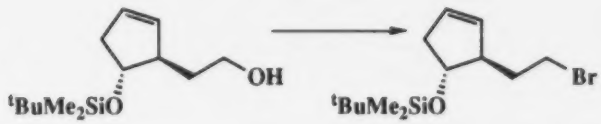


144 **145**

A solution of aldehyde **144** (299.5 mg, 1.25 mmol) in THF (4 mL plus 1 mL as a rinse) was added at room temperature to a stirred suspension of lithium aluminum hydride (95 mg, 2.49 mmol) in THF (5 mL). The mixture was stirred for 15 min and then quenched by successive addition of water (0.1 mL), 15% aqueous sodium hydroxide (0.1 mL), and water (0.3 mL). Stirring was continued for 30 min and the mixture was then filtered through a pad (3 x 2 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 14 cm), using 15% ethyl acetate-hexane, afforded alcohol **145** (269.2 mg, 89%) as a pure [TLC, silica, 15% ethyl acetate-hexane], colorless oil: FTIR (CH_2Cl_2 cast) 3346, 2954, 2929, 2898, 2887, 2857, 1472, 1463, 1361, 1256, 1112, 1099, 1069, 882, 836, 775, 709 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.50-1.77 (m, 2 H), 2.06 (br s, 1 H), 2.15-2.30 (m, 1 H), 2.49-2.70 (m, 2 H), 3.6-3.79 (m, 2 H), 4.04-4.16 (m, 1 H), 5.53-5.64 (m, 2 H); ^{13}C NMR ($CDCl_3$

50.3 MHz) δ -4.71, -4.16, 18.04, 25.88, 36.31, 41.60, 51.19, 61.51, 79.52, 127.90, 132.89; exact mass *m/z* calcd for $C_9H_{17}O_2Si$ [M - *t*-Bu] 185.0998, found 185.0996. An analytical sample was prepared by Kugelrohr distillation (120°C, 14 mm Hg). Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.74; H, 10.63.

trans (1,1-Dimethylethyl)dimethyl[[2-(2-bromoethyl)-cyclopent-3-en-1-yl]oxy]silane (146).

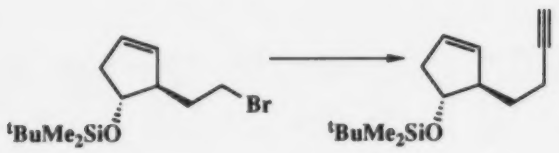


145 **146**

Triphenylphosphine (582.5 mg, 2.22 mmol) and carbon tetrabromide (736.5 mg, 2.22 mmol) were added successively to a cold (0°C) and stirred solution of alcohol **145** (269.2 mg, 1.11 mmol) in dichloromethane (15 mL). The cooling bath was removed and, after 30 min, the mixture was filtered through a pad (3 x 2 cm) of silica gel using dichloromethane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 14 cm), using first hexane and then 5% ethyl acetate-hexane, gave bromide **146** (326.4 mg, 96%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2955, 2929, 2895, 2857, 1472, 1256, 1110, 1086, 904, 875, 837, 775, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.84 (s, 9 H), 1.72-2.09 (m, 2 H), 2.15-2.29

(m, 1 H), 2.50-2.74 (m, 2 H), 3.42 [td, J = 7.5, 1.0 Hz (includes s (1 H) at δ 3.415) 2 H], 4.06 (dt, J = 7.0, 4.5 Hz, 1 H), 5.56-5.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.64, -4.32, 18.07, 25.91, 31.39, 36.97, 41.69, 53.43, 78.60, 128.69, 131.38; exact mass m/z calcd for $C_9H_{16}OBrSi$ (M - *t*-Bu) 247.0154, found 247.0148. An analytical sample was prepared by Kugelrohr distillation (110°C, 15 mm Hg). Anal. Calcd for $C_{13}H_{25}OBrSi$: C, 51.14; H, 8.25. Found: C, 51.27; H, 8.36.

***trans* (1,1-Dimethylethyl)dimethyl[[2-(3-butynyl)-cyclopent-3-en-1-yl]oxy]silane (147).**

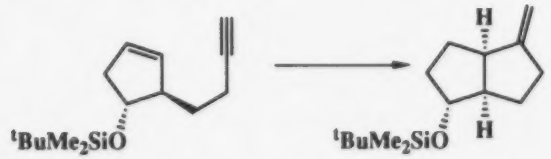


146 **147**

Acetylene [purified by passage through a cold trap (-78°C), a bubbler containing concentrated sulfuric acid, a tube (15 x 2 cm) packed with sodium hydroxide pellets, and then a tube (26 x 1.5 cm) packed with Drierite] was bubbled through cold (-78°C) THF (10 mL) for 12 min. *n*-BuLi (1.1 mL, 1.6 M in hexanes, 1.75 mmol) was added dropwise and the resulting mixture was stirred for 10 min. Bromide **146** (178.3 mg, 0.58 mmol) in tetrahydrofuran (2 mL plus 1 mL as a rinse) was then added, followed by hexamethylphosphoramide (1.0 mL). The cooling bath was removed and stirring was continued for

for 3 h. The mixture was then quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% dichloromethane-hexane, afforded enyne **147** (130.5 mg, 89%) as a pure [^1H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 3313, 2955, 2929, 2889, 2857, 1472, 1463, 1361, 1256, 1111, 1093, 1071, 1006, 905, 875, 836, 815, 775, 710, 631 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.39-1.76 (m, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.14-2.27 (m, 3 H), 4.05 (dt, J = 6.7, 4.4 Hz, 1 H), 5.64 (s, 2 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ -4.63, -4.35, 16.84, 18.11, 25.94, 32.32, 42.00, 53.80, 68.33, 78.50, 84.49, 128.41, 132.10; exact mass *m/z* calcd for $C_{11}H_{17}OSi$ (M - *t*-Bu) 193.1049, found 193.1039. An analytical sample was prepared by Kugelrohr distillation (105°C, 14 mm Hg). Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 72.16; H, 10.60.

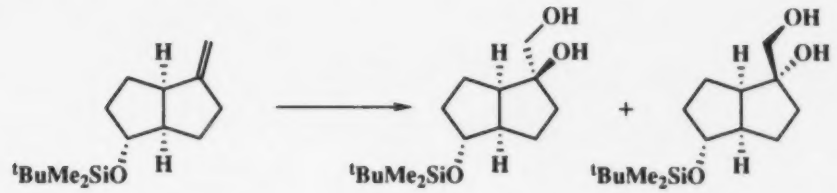
(1,1-Dimethylethyl)dimethyl[[(1α,3aα,6aα)-octa-hydro-4-methylenepentalen-1-yl]oxy]silane (149).



147 **149**

Triethylborane (0.80 mL, 1.0 M in hexane, 0.80 mmol) was added dropwise to a stirred solution of enyne **147** (201.4 mg, 0.80 mmol) and tributyltin hydride (0.27 mL, 1.00 mmol) in hexane (55 mL). The mixture was stirred at room temperature for an arbitrary period of 3 h (protection from atmospheric moisture by a Drierite tube). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 14 cm), using first hexane followed by 10% dichloromethane-hexane, gave olefin **149** (154.2 mg, 76%; 85% after correction for recovered starting material) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2936, 2930, 2894, 2857, 1472, 1462, 1361, 1255, 1179, 1122, 1092, 1063, 1025, 1006, 880, 866, 835, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.13-1.91 (m, 5 H), 1.98-2.45 (m, 4 H), 2.86-3.02 (m, 1 H), 3.86 (dd, J = 3.5, 3.5 Hz, 1 H), 4.73 (dddd, J = 2.0, 2.0, 2.0, 2.0 Hz, 1 H), 4.81 (dddd, J = 2.0, 2.0, 2.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.64, -4.54, 18.17, 25.94, 29.33, 30.79, 34.27, 34.94, 46.29, 53.43, 80.00, 104.19, 158.47; exact mass *m/z* calcd for $C_{15}H_{28}OSi$ 252.1909, found 252.1905. An analytical sample was prepared by Kugelrohr distillation (126°C, 14 mm Hg). Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 71.51; H, 11.15.

(1α,3aβ,4β,6aβ)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-1-(hydroxymethyl)pentalen-1-ol (150a) and (1α,3aα,4α,6aα)-4-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]octahydro-1-(hydroxymethyl)pentalen-1-ol (150b).



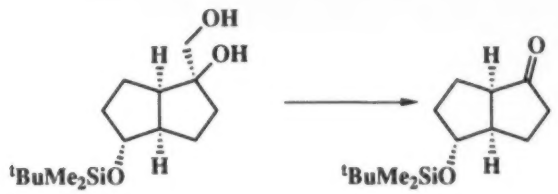
149 **150a** **150b**

Osmium tetroxide (3.4 mL, 2.5 w/w% in 2-methyl-2-propanol, 0.27 mmol) was added dropwise to a stirred solution of olefin **149** (687.0 mg, 2.72 mmol) in acetone (2.5 mL) and water (5.0 mL). 4-Methylmorpholine *N*-oxide monohydrate (735.3 mg, 5.44 mmol) was added in one portion and stirring was continued for 3 h. The mixture was saturated with $MgSO_4$ and filtered through a pad (5 x 3 cm) of silica gel using ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 50% ethyl acetate-hexane, afforded diols **150** (787.7 mg, 99%) as a mixture of two diastereomers in a 12:1 ratio (^1H NMR). The diastereomers were separated by flash chromatography over silica gel (3 x 25 cm), using ethyl acetate-hexane mixtures containing from 35 to 50% ethyl acetate. The minor diastereoisomer **150b** had: FTIR (CH_2Cl_2 cast) 3385, 2953, 2894, 2885, 2857, 1472, 1463, 1254, 1117,

1097, 1064, 1022, 1006, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 6 H), 0.86 (s, 9 H), 1.18-1.88 (m, 8 H), 2.0 (br s, 2 H), 2.2-2.4 (m, 2 H), 3.48 (s, 2 H), 3.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.64, -4.55, 18.12, 23.56, 25.91, 27.52, 36.01, 36.46, 47.81, 52.86, 69.53, 80.49, 82.40; exact mass *m/z* calcd for $C_{15}H_{30}O_3Si$ 286.1964, found 286.1966. An analytical sample was prepared by Kugelrohr distillation (164°C, 14 mm Hg). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.01; H, 10.52.

The major diastereoisomer **150a** had: FTIR (CH_2Cl_2 cast) 3376, 2954, 2935, 2930, 2885, 2857, 1472, 1463, 1372, 1255, 1119, 1094, 1067, 1052, 1005, 862, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.99-1.19 (m, 1 H), 1.30-2.20 [m (includes br s at δ 1.95), 9 H], 2.35-2.58 (m, 2 H), 3.58 (d, J = 11 Hz, 1 H), 3.67 (d, J = 11 Hz, 1 H), 3.75-3.84 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) -4.59, 18.08, 25.54, 25.87, 27.78, 33.92, 35.65, 51.26, 52.03, 66.96, 81.15, 84.89; exact mass *m/z* calcd for $C_{15}H_{30}O_3Si$ 286.1964, found 286.1965. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.83; H, 10.61.

(3aα,4α,6aα)-4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]hexahydro-1-pentalenone (151).

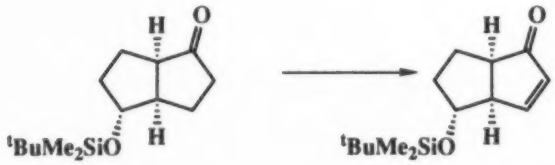


150ab **151**

Potassium carbonate (127.8 mg, 0.92 mmol) and lead tetraacetate (273.3 mg, 0.62 mmol) were added successively to a stirred and cooled (0°C) solution of diols **150a** and **150b** (88.3 mg, 0.31 mmol) in dichloromethane (10 mL). After 10 min the cold bath was removed and stirring was continued for 50 min. The mixture was then filtered through a pad (3 x 2 cm) of silica gel using ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 5% ethyl acetate-hexane, gave ketone **151** (73.0 mg, 93%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2956, 2929, 2885, 2857, 1740, 1472, 1463, 1254, 1178, 1141, 1119, 1098, 1064, 1021, 1005, 884, 869, 836, 812, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.36-1.82 (m, 4 H), 2.0-2.40 (m, 4 H), 2.54-2.76 (m, 2 H), 3.90-4.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.78, -4.63, 18.04, 2397, 25.80, 26.52, 34.51, 37.96, 49.97, 50.12, 79.44, 222.64; exact mass *m/z* calcd for $C_{14}H_{26}O_2Si$ 254.1702, found 254.1696. An analytical sample was prepared by Kugelrohr distillation (152°C, 15 mm Hg). Anal.

Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 65.90; H, 10.48.

(3aα,4α,6aα)-4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-4,5,6,6a-tetrahydro-1(3a*H*)-pentalenone (153)[73].



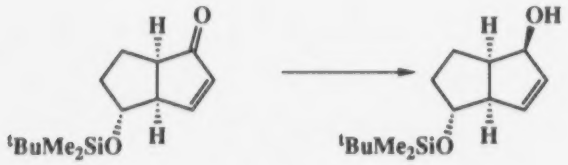
151 **153**

A solution of ketone **151** (198.9 mg, 0.78 mmol) in THF (2 mL plus 1 mL as a rinse) was added to a stirred and cooled (-78°C) solution of lithium diisopropylamide [prepared by addition of *n*-butyllithium (0.98 mL, 1.6 M in hexanes, 1.56 mmol) to a stirred and cooled (-78°C) solution of diisopropylamine (0.22 mL, 1.56 mmol) in THF (10 mL)]. After 30 min the mixture was transferred by cannula to a stirred solution of diphenyl disulfide (204.3 mg, 0.94 mmol) in THF (3 mL) and HMPA (1.0 mL). After 1.5 h the mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and 0.5 M HCl (10 mL). The layers were separated and the organic phase was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to give the crude sulfides as a yellow oil. The oil was taken up in dichloromethane (15 mL) and solid sodium bicarbonate (120.0 mg, 1.43 mmol) was added. The mixture was cooled to -78°C and MCPBA (175.4 mg, 80-85%, 0.84 mmol) added in one portion with stirring. The cold bath

was removed and the mixture allowed to attain room temperature. Additional MCPBA (55 mg and then 50 mg, 0.50 mmol total) was added so that all the sulfide had been oxidized (TLC control, silica, 10% ethyl acetate-hexane). The mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and 10% aqueous sodium sulfite (10 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 x 10 mL), and brine. The combined aqueous washes were extracted once with ethyl acetate. All of the organic extracts were combined, dried ($MgSO_4$) and evaporated. The crude sulfoxides were taken up in toluene (15 mL) and trimethyl phosphite (0.18 mL, 1.56 mmol) was added. The resulting mixture was refluxed for 5 h, cooled, and filtered through a pad (3 x 2 cm) of silica gel using hexane. The filtrate was discarded and the pad was washed with ethyl acetate. Evaporation of the resulting filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 5% ethyl acetate-hexane, gave enone **153** (143.1 mg, 73%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2955, 2929, 2857, 1714, 1437, 1254, 1142, 1095, 1075, 1054, 1043, 1009, 832, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 1.24-1.46 (m,1 H), 1.48-1.63 (m, 1 H), 1.74-1.89 (m, 1 H), 2.02-2.27 (m, 1 H), 2.79 (ddd, J = 10.0, 5.5, 1.5 Hz, 1 H), 3.13-3.22 (m, 1 H), 4.10 (br d, J = 4.0 Hz, 1 H), 6.10 (dd, J = 5.5, 2.0 Hz, 1 H), 7.54 (dd, J = 5.5, 3.0 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.82, -4.66, 18.04, 25.79, 26.68, 32.73, 48.62, 57.62,

75.09, 135.36, 163.88, 212.95; exact mass *m/z* calcd for $C_{14}H_{24}O_2Si$ 252.1545, found 252.1539. An analytical sample was prepared by Kugelrohr distillation (90°C, 0.10 mm Hg). Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.90; H, 9.36.

(1α,3aβ,4β,6aβ)-4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-1,3a,4,5,6,6a-hexahydro-1-pentalenol (156).

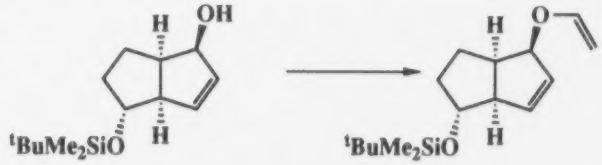


153 **156**

Sodium borohydride (214.5 mg, 5.67 mmol) was added to a stirred and cooled (water bath at room temperature) mixture of enone **153** (143.1 mg, 0.57 mmol) and cerium trichloride heptahydrate (211.2 mg, 0.57 mmol) in methanol (10 mL). After 15 min the reaction was quenched by addition of water and the mixture was extracted with ethyl acetate (3 x 25 mL). The aqueous layer was acidified with 0.5 M hydrochloric acid and extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10% ethyl acetate-hexane, gave allylic alcohol **156** (131.4 mg, 91%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 3330, 2955, 2929, 2886, 2857, 1472, 1463, 1361, 1255, 1092, 1054, 1028, 1005, 993, 907, 861, 883,

812, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.43-1.85 (m, 5 H), 2.83-3.01 (m, 2 H), 3.98 (td, J = 4.0, 1.5 Hz, 1 H), 4.77-4.86 (m, 1 H), 5.66 (dt, J = 5.5, 2.0 Hz, 1 H), 5.78 (dt, J = 5.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.71, -4.60, 18.14, 22.78, 25.90, 35.54, 43.76, 60.90, 77.84, 78.42, 134.44, 134.57; exact mass *m/z* calcd for $C_{10}H_{17}O_2Si$ (M - *t*-Bu) 197.0998, found 197.0993. An analytical sample was prepared by Kugelrohr distillation (80°C, 0.06 mm Hg). Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 65.89; H, 10.50.

Ethenyl (±)-(1α,3aβ,4β,6aβ)-1-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,3a,4,5,6,6a-hexahydropentalen-1-yl] ether (160).

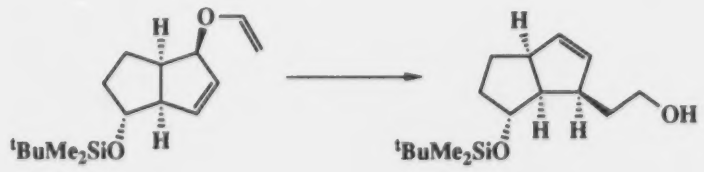


156 **160**

Sodium acetate (25.3 mg, 0.31 mmol) and mercuric acetate (49.2 mg, 0.15 mmol) were added to a stirred solution of alcohol **156** (39.3 mg, 0.15 mmol) in freshly distilled ethyl vinyl ether (12 mL). The resulting suspension was refluxed for 48 h and then cooled to room temperature. Anhydrous potassium carbonate was added to the mixture and the excess of ethyl vinyl ether was evaporated. The residue was taken up in dichloromethane-hexane (2:3) and filtered through a pad

(2 x 3 cm) of silica gel. The filtrate was evaporated to give vinyl ether **160** (26.8 mg, 72%) as a colorless oil containing trace impurities [^{1}H NMR]: FTIR (CH_2Cl_2 cast) 2955, 2929, 2886, 2857, 1635, 1610, 1472, 1463, 1362, 1320, 1254, 1193, 1157, 1093, 1055, 1005, 987, 961, 945, 907, 863, 834, 813, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 1.35-1.80 [m (includes t at δ 1.71, J = 5.0 Hz), 4 H], 2.89-3.13 (m, 2 H), 3.96-4.04 (m, 2 H), 4.24 (dd, J = 14.0, 2.0 Hz, 1 H), 4.87 (dd, J = 8.0, 1.5 Hz, 1 H), 5.68 (dt, J = 5.5, 2.0 Hz, 1 H), 5.82 (dt, J = 5.5, 2.0 Hz, 1 H), 6.43 (dd, J = 14.0, 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.71, -4.59, 18.12, 23.01, 25.90, 35.21, 42.79, 60,86, 78.28, 84.09, 87.58, 131.20, 135.36, 151.45; exact mass *m/z* calcd for $C_{14}H_{25}OSi$ (M - C_2H_3O) 237.1675, found 237.1670. A satisfactory combustion analysis could not be obtained.

(1α,3aβ,6β,6aβ)-[6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,3a,4,5,6,6a-hexahydro-1-pentalene]-ethanol (162).

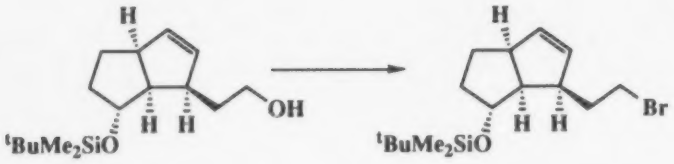


160 **162**

Triisobutylaluminum (0.38 mL, 1.0 M in toluene, 0.38 mmol) was added to a cooled (-78°C) and stirred solution of

vinyl ether **160** (26.8 mg, 0.096 mmol) in dichloromethane (4.0 mL). The cold bath was removed and, after 1 h, the mixture was recooled to -78°C and quenched by addition of 0.5 M hydrochloric acid. The mixture was then poured into a separatory funnel containing 0.5 M hydrochloric acid and ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10-15% ethyl acetate-hexane, gave alcohol **162** (25.7 mg, 95%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 3360, 2953, 2932, 2884, 2857, 1472, 1463, 1372, 1361, 1152, 1103, 1053, 1006, 836, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.16-1.73 (m, 4 H), 1.79-2.05 (m, 2 H), 2.05-2.33 (m, 1 H), 2.56 (td, J = 8.5, 5.5 Hz, 1 H), 2.79-2.98 (m, 1 H), 3.11-3.28 (m, 1 H), 3.61-3.88 (m, 2 H), 4.05 (q, J = 6.0 Hz, 1 H), 5.41-5.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.44, -3.94, 18.04, 25.94, 27.81, 33.04, 35.36, 44.36, 48.94, 53.17, 63.02, 75.33, 132.83, 137.43; exact mass *m/z* calcd for $C_{12}H_{21}O_2Si$ (M - *t*-Bu) 225.1311, found 225.1314.

(1α,3aα,6β,6aα)-[(1,1-Dimethylethyl)dimethyl [[6-(2-bromoethyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl]oxy]-silane (163).

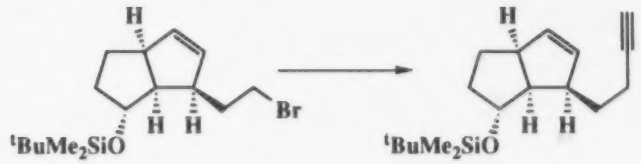


162 **163**

Triphenylphosphine (1.0467 g, 4.0 mmol) and carbon tetrabromide (1.3235 g, 4.0 mmol) were added successively to a cooled (0°C) and stirred solution of alcohol **162** (563.7 mg, 2.0 mmol) in dichloromethane (25 mL). The cold bath was removed and, after 30 min, the reaction mixture was filtered through a pad (3 x 2 cm) of silica gel using dichloromethane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 5% dichloromethane-hexane, gave bromide **163** (658.9 mg, 96%) as a pure [TLC], colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2929, 2884, 2856, 1742, 1462, 1475, 1362, 1256, 1111, 1103, 1049, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.20-1.39 (m, 1 H), 1.47-1.65 (m, 2 H), 1.82-2.00 (m, 2 H), 2.12-2.23 (m, 1 H), 2.54 (td, *J* = 8.5, 5.0 Hz, 1 H), 2.91-3.00 (m, 1 H), 3.18-3.26 (m, 1 H), 3.45-3.59 (m, 2 H), 4.04 (ddd, *J* = 5.0, 5.0, 5.0 Hz, 1 H), 5.47 (ddd, *J* = 5.5, 2.0, 2.0 Hz, 1 H), 5.53 (ddd, *J* = 5.5, 2.6, 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.52,

-3.90, 17.97, 25.94, 28.02, 33.03, 34.17, 35.36, 45.93, 49.10, 52.74, 75.08, 131.22, 135.25; exact mass *m/z* calcd for $C_{12}H_{20}O_1SiBr$ (M - *t*-Bu) 287.0467, found 287.0459.

(1α,3aα,6β,6aα)-(1,1-Dimethylethyl)dimethyl [[6-(3-butynyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl]oxy]-silane (164).

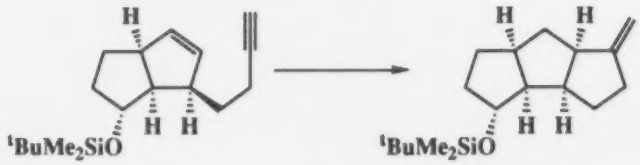


163 **164**

Acetylene [purified by passage through a cold trap (-78°C), a bubbler containing concentrated sulfuric acid, a tube (15 x 2 cm) packed with sodium hydroxide pellets, and then a tube (26 x 1.5 cm) packed with Drierite] was bubbled through cold (-78°C) THF (30 mL) for 20 min. *n*-BuLi (3.6 mL, 1.6 M in hexanes, 5.72 mmol) was added dropwise and the resulting mixture was stirred for 15 min. Bromide **163** (658.9 mg, 1.91 mmol) in THF (5 mL plus 2 mL as a rinse) was then added, followed by hexamethylphosphoramide (4 mL). The cooling bath was removed and stirring was continued for for 1 h. The mixture was quenched with water and extracted with hexane. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% dichloromethane-hexane, gave enyne **164** (517.6 mg, 93%) as a pure [^{1}H NMR], colorless oil: FTIR

(CH_2Cl_2 cast) 3313, 2953, 2930, 2892, 2885, 2856, 2105, 1472, 1462, 1361, 1256, 1103, 1068, 1053, 1026, 1006, 836, 774, 632 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 1.23-1.40 (m, 1 H), 1.40-1.62 (m, 3 H), 1.73-2.02 [m (includes t at δ 1.95, *J* = 3.0 Hz), 3 H], 2.23-2.36 (m, 2 H), 2.52 (ddd, *J* = 8.5, 4.5, 4.5 Hz, 1 H), 2.82-2.97 (m, 1 H), 3.14-3.29 (m, 1 H), 4.05 (ddd, *J* = 4.5, 4.5, 4.5 Hz, 1 H), 5.49 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -4.53, -3.99, 18.17, 25.98, 28.27, 29.91, 35.28, 46.60, 49.50, 53.11, 68.39, 75.19, 84.56, 132.19, 134.64; exact mass *m/z* calcd for $C_{14}H_{21}OSi$ (M - *t*-Bu) 233.1362, found 233.1363. An analytical sample was prepared by Kugelrohr distillation (118°C, 11 mm Hg). Anal. Calcd for $C_{18}H_{30}OSi$: C, 74.42; H, 10.41. Found: C, 74.56; H, 10.54.

(1α,2α,3α,6α,8α)-(1,1-Dimethylethyl)dimethyl[[9-methylenetricyclo[6.3.0.$0^{2,6}$]undecan-3-yl]oxy]silane (159).



164 **159**

Tributyltin hydride (73 µl, 0.27 mmol) and AIBN (4.2 mg, 0.026 mmol) were added to a solution of enyne **164** (58.1 mg, 0.20 mmol) in toluene (10 mL) and the mixture was refluxed for 45 min, cooled and evaporated. Flash chromatography of

the residue over silica gel (2 x 16 cm), using 5% dichloromethane-hexane, gave olefin **159** (46.4 mg, 79%) as a pure [^{1}H NMR], colorless oil: FTIR (CH_2Cl_2 cast) 2949, 2936, 2898, 2858, 1471, 1462, 1254, 1110, 1068, 1048, 1036, 901, 878, 854, 835, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 0.97-1.02 (m, 1H), 1.23-1.32 (m, 5 H), 2.25-2.37 (m, 1H), 2.38-2.49 (m, 2 H), 2.53-2.73 (m, 2 H), 2.84 (dd, J = 18.0, 9.0 Hz, 1H), 4.05 (dd, J = 8.0, 4.0 Hz, 1H), 4.71-4.74 (m, 1H), 4.76-4.79 (m, 1H); ^{13}C NMR ($CDCl_3$ 100.6 MHz) δ -4.7, -4.4, 18.15, 25.96, 27.08, 29.32, 34.60, 37.16, 39.17, 45.85, 47.06, 52.80, 55.97, 76.14, 104.42, 156.39; exact mass *m/z* calcd for $C_{18}H_{32}OSi$, found 292.2218. An analytical sample was prepared by Kugelrohr distillation (125°C, 11 mm Hg). Anal. Calcd. for $C_{18}H_{32}OSi$: C, 73.90; H, 11.03. Found: C, 73.76; H, 11.18.

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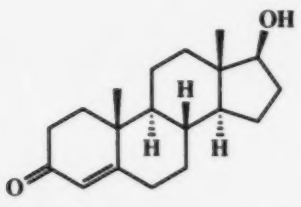
CHAPTER 2

FREE RADICAL METHODOLOGY:

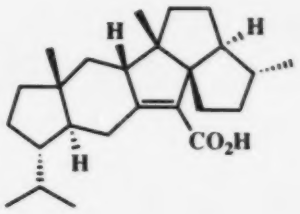
FORMATION OF TRANS RING-FUSED COMPOUNDS

I. INTRODUCTION

The bicyclo[4.3.0]nonane (hydrindane) nucleus is widely encountered in a variety of naturally occurring compounds, particularly steroids (e.g., testosterone **1**) and terpenes (e.g., retigeranic acid **2**).

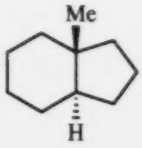


1 testosterone



2 retigeranic acid

The angularly methylated *trans* hydrindane **3** is of particular interest because it contains the structural and stereochemical features found in the C and D rings of many steroidal hormones.[1] As a result, quite a number of different procedures have been developed for constructing *trans* hydrindanes in a stereocontrolled manner.

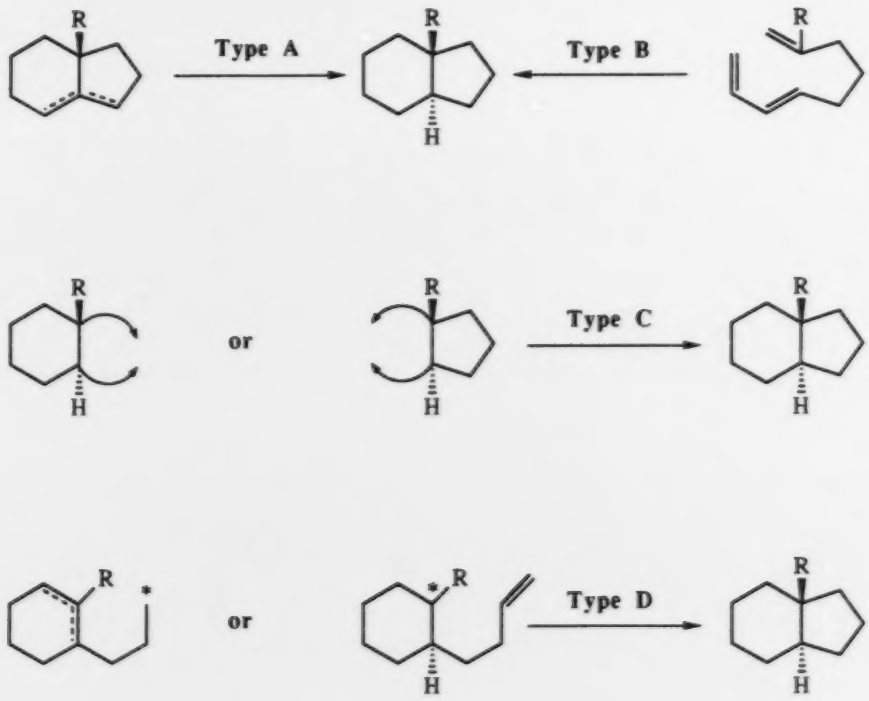


3

This review surveys the modern approaches to this important structural subunit. The treatment does not attempt

to provide comprehensive coverage of the literature, but focuses on selective examples which highlight the various stategies that have evolved.[2] These strategies (see Scheme **1**) may be divided into four basic types (A, B, C and D).

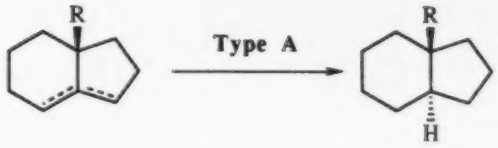
Scheme 1



It is noteworthy that in routes of type B and D control of the ring-junction stereochemistry is achieved at the stage of hydrindane ring formation.

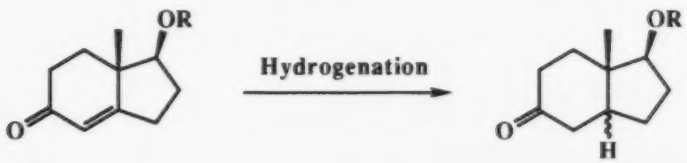
Type A Approaches

Scheme 2



In Type A routes to *trans* hydrindanes the ring junction stereochemistry is controlled by reduction of an sp^2 center at the angular position. This has been accomplished by a variety of methods including (1) catalytic hydrogenation,[3] (2) dissolving metal or hydride reduction of α,β unsaturated enones,[4] and (3) directed reduction of allylic alcohol derivatives.[5]

Table 1



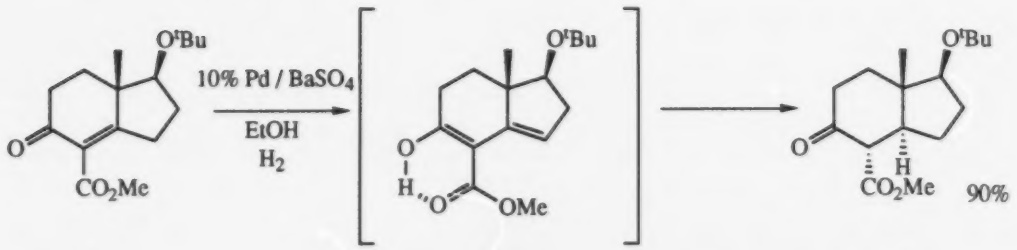
		solvent	cis : trans
4a R = H	5% Pd / $CaCO_3$	EtOH	100 : 0
4b R = ^{t}Bu	5% Pd / C	C_6H_{14}	63 : 27

Parrish[3a,b] has examined the catalytic hydrogenation of hydrindenones **4a** and **4b** (Table **1**) and has found that *cis*

hydrindanones are produced on reduction with hydrogen and palladium on calcium carbonate. If one face of the cyclopentane ring is blocked with a bulky *tert*-butyl ether then some of the *trans* product is formed.

If, however, the enone is derivatised (Scheme **3**) as the β-ketoester **5**, hydrogenation leads to a 90% yield of the *trans* hydrindanone **7**. The author suggests that hydrogenation occurs via the enol form of the β-ketoester **6**.

Scheme 3

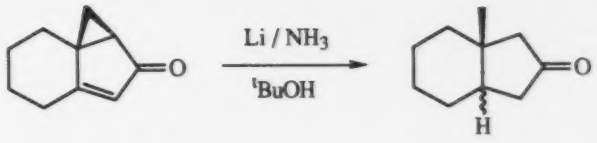


5 **6** **7**

Dissolving metal reduction of the cyclopropyl ketone **8**, using lithium in liquid ammonia (Scheme **4**), was not stereoselective.[4b] In this example a 7:3 ratio of the two hydrindanones **9** was obtained with the *cis* product predominating.

The conjugate reduction of the enone **10** with lithium in liquid ammonia (Scheme **5**) gave the hydrindanone **11** as a

Scheme 4



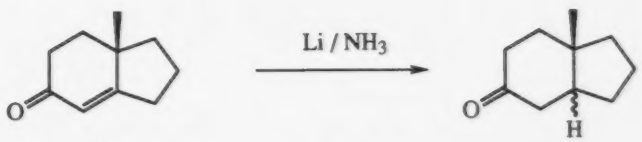
8 **9**

cis : trans

7 : 3

mixture of isomers, again with the *cis* compound predominating (*cis*:*trans* = 9:1).[4b]

Scheme 5



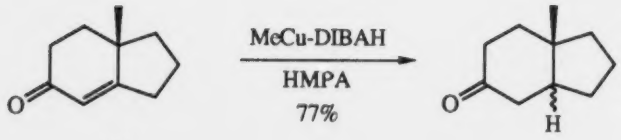
10 **11**

cis : trans

9 : 1

Saegusa[4c] has found, however, that the stereoselectivity can be reversed (Scheme **6**) if conjugate reduction is carried out using a reagent prepared by adding methylcopper(I) to a solution of diisobutylaluminum hydride in HMPA. If an excess of MeCu is used a 9:1 mixture (*trans:cis*) of the hydrindanone **12** is obtained in 77% yield. The reduction may proceed by the in situ formation of Cu-H like reagent.

Scheme 6



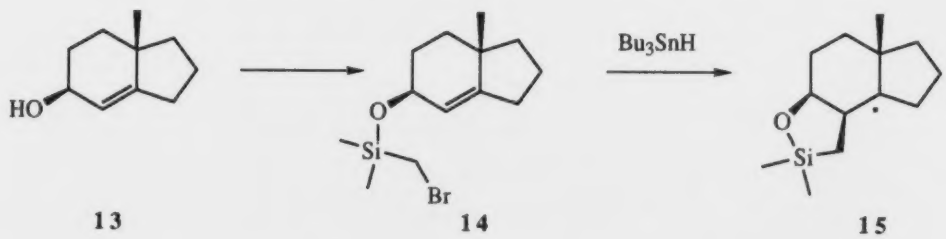
10 **12**

cis : trans
1 : 9

Stork[5a,b] and Mandai[5c] have described elegant methods for stereospecific generation of *cis* or *trans* ring junctions in hydrindane and decalin compounds using allylic alcohol derivatives.

The first method developed by Stork (Scheme **7**), involves radical cyclization of the (bromomethyl)dimethylsilyl ether

Scheme 7



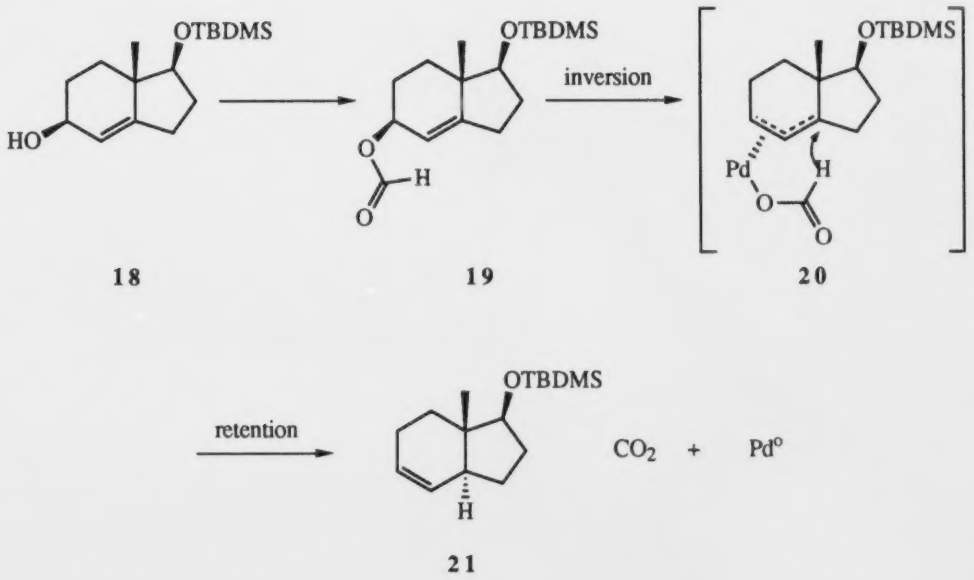
13 **14** **15**

16 **17**

of the allylic alcohol **13**. The stereochemistry of the final hydroxymethyl substituent is dictated by the *cis* nature of the radical cyclization **14→15**, and the *trans* hydrindane **16** is then formed by hydrogen atom abstraction of the angular radical on the less hindered face of the tricyclic intermediate **15**. The cyclic silyl ether **16** can undergo either protiolytic or oxidative cleavage of the carbon-silicon bond.

Mandai's procedure (Scheme **8**) begins with the formyl ester derivative of allylic alcohol **18**. Palladium catalyzed hydrogenolysis of the allylic formate **19** proceeds via π-allyl palladium complex **20** whose formation involves inversion of

Scheme 8

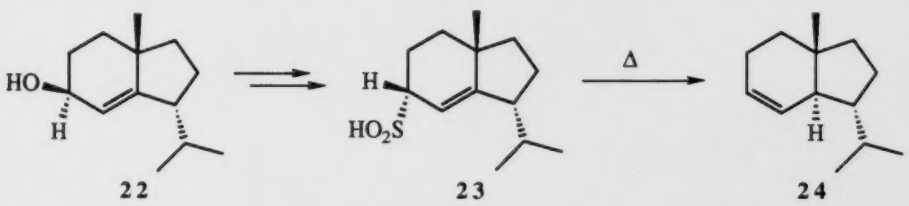


the formate stereochemistry. The subsequent migration of the hydride from the palladium formate complex to the angular carbon occurs suprafacially; therefore, overall inversion results.

In both Stork's and Mandai's procedures *cis* hydrindanes can be produced by simply inverting the configuration of the allylic alcohol.

Corey[5d] has also developed a method (Scheme **9**) for the stereospecific synthesis of *trans* hydrindanes. His procedure depends on internal delivery of hydrogen to the sp^2 carbon at the ring junction. Thermal decomposition of the sulfinic acid **23** (~40-50°) gave the unsaturated hydrindane **24** in excellent yield. The sulfinic acid was readily prepared from

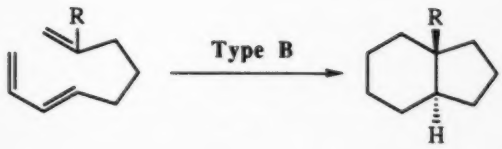
Scheme 9



the allylic alcohol **22** by the sequence: (1) Mitsunobu inversion with thiolacetic acid (82%), (2) reduction of the thiolacetate to the thiol with $LiAlH_4$ (95%), and (3) oxidation with 2 equivalents of *m*-chloroperoxybenzoic acid.

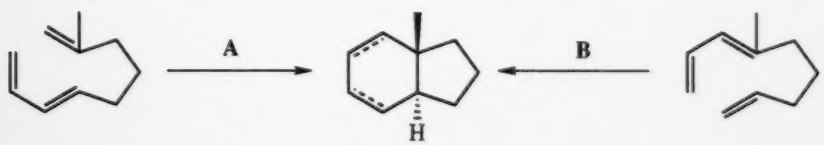
Type B Approaches

Scheme 10



Intramolecular Diels-Alder reactions are a particularly attractive method for the preparation of *trans* hydrindanes because the ring junction stereochemistry is achieved at the stage of hydrindane ring formation. In principle, two different intramolecular Diels-Alder sequences (Scheme **11**) could be used to prepare the desired ring system. In pathway **A**, the incipient angular methyl group would be introduced as part of the dienophile, whereas in **B** the angular methyl group would originate as a butadiene substituent. Trisubstituted dienes, as needed for route **B**, experience severe steric congestion, thus limiting their application.[6j]

Scheme 11



In the case of angularly methylated hydrindanes, however, high stereocontrol is rather difficult to obtain.

Jung[6a,h] and Sutherland[6r] (Scheme 12) have found that the *cis* fused hydrindane **26** was the predominant product in the 4+2 cycloaddition of the triene **25**.

Scheme 12

25 **26** 99%

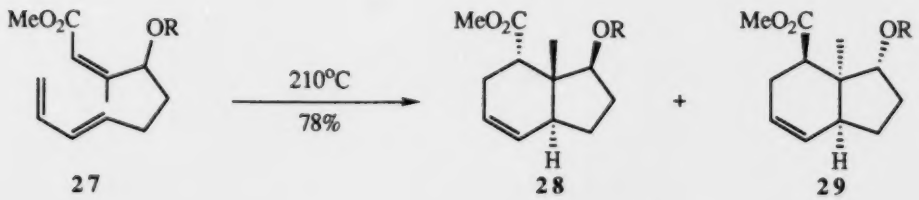
cis : trans

70 : 30

Improvement in the *cis:trans* ratio was obtained when the ketone was protected as its ethylene ketal (*cis:trans* = 25:75).[6a]

Roush[6c] has found (Scheme **13**) that maximum selectivity is achieved with terminally activated dienophiles such as **27**. In this case *trans* and *cis* hydrindanes were formed in a 4:1 ratio in 78% yield. This reversal in stereoselectivity

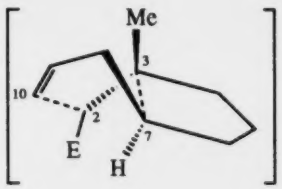
Scheme 13



27 **28** **29**

4 : 1

by a terminally activated dienophile, as in **27**, has been explained on the basis of a concerted but nonsynchronous mechanism. Hence bonding between carbons 3 and 7 should precede bonding between carbons 2 and 10 (see **30**). Under these circumstances, a cyclopentane-like species is formed early in the transition state and leads preferentially to *trans* adducts.



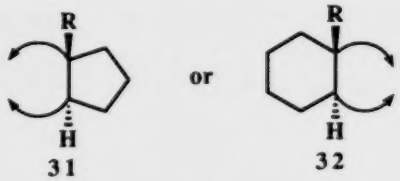
30

Despite the fact that complete stereochemical control is difficult to achieve, intramolecular Diels-Alder chemistry has remained very popular, due to the efficiency with which the *trans* hydrindane ring system is built up.[6]

Type C Approaches

Scheme 14

The most utilized approach to the synthesis of *trans* hydrindanes involves the attachment to a ring of two pendants that are adjacent and *trans* to one another. The ends of the two pendants are then brought together, forming the hydrindane system. The two pendants can be first attached to the five membered ring, followed by cyclization to form the six membered ring (**31**) or one can begin with two pendants attached to a six membered ring (**32**).

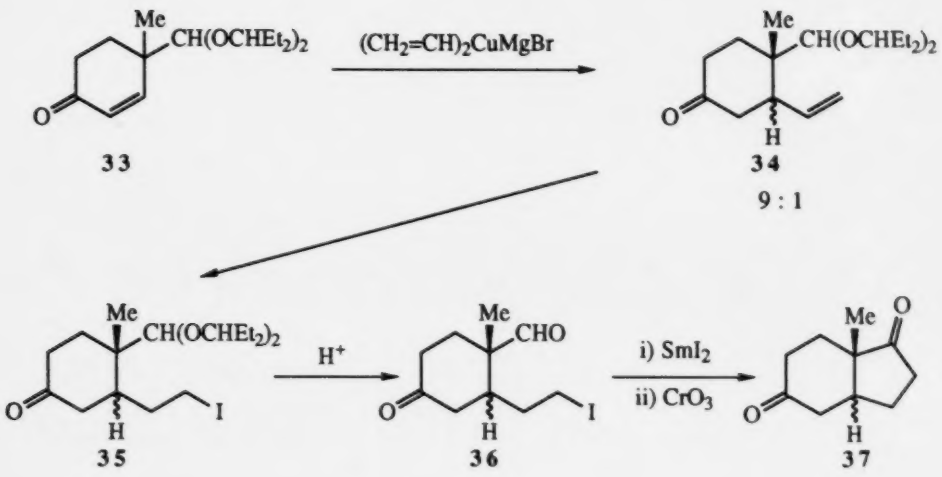


31 **32**

This type of approach therefore depends on methods of preparing ring systems containing two adjacent pendants that are *trans* to one another and that contain suitable functionality so that the ends of the pendants may be joined to form the second ring.

One such method incorporates, as the key step, organocuprate conjugate addition to γ-substituted cyclohexenones.[7] For example, Zoretic[7e] added a vinyl cuprate to the cyclohexenone **33** giving a 9:1 mixture of two inseparable diastereomers in which the major component has the vinyl group and the acetal pendant *trans* (Scheme **15**). This type of approach exploits the preference for diequatorial placement of large groups on six membered rings.

Scheme 15

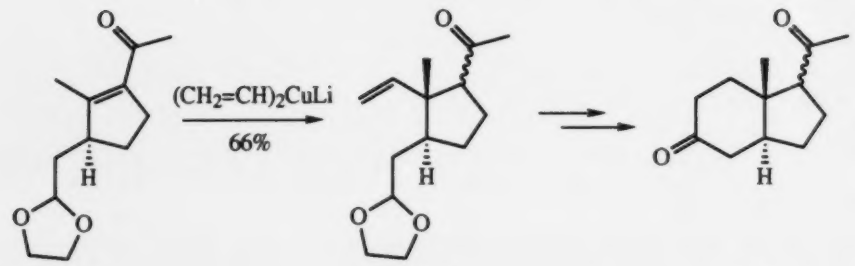


With the stereochemistry of the ring juncture secured, the task of closing the D ring (using steroid nomenclature) remained. This was accomplished as follows: Hydroboration of the double bond, followed by oxidative workup, gave an alcohol which was converted into the primary iodide **35**. Removal of the acetal protecting group gave the iodo-aldehyde **36**, which underwent radical cyclization upon treatment with SmI_2.[8] Subsequent Jones oxidation afforded the diketone **37**. The material was contaminated with a small amount of the *cis* isomer.

A variation of this theme involves conjugate addition of organocuprates to five membered rings.[7f] The addition of divinylcuprate to enone **38** occurred from the less hindered face (opposite to the acetal-carrying chain) to give **39** in

66% yield as a 9:1 mixture of *trans* and *cis* isomers (Scheme **16**).

Scheme 16



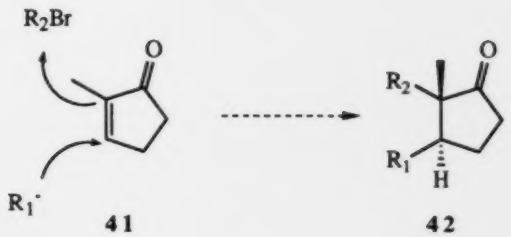
38 **39** **40**

trans : cis
9 : 1

All that remained was to bring the ends of the two pendants together to close the 6 membered ring. This was accomplished by first hydroboration of the double bond and conversion of the resulting alcohol into a good leaving group by tosylation. The acetal was then deprotected and transformed into a cyanohydrin which, upon treatment with strong base, resulted in displacement of the primary tosylate and formation of the *trans* hydrindane **40**.

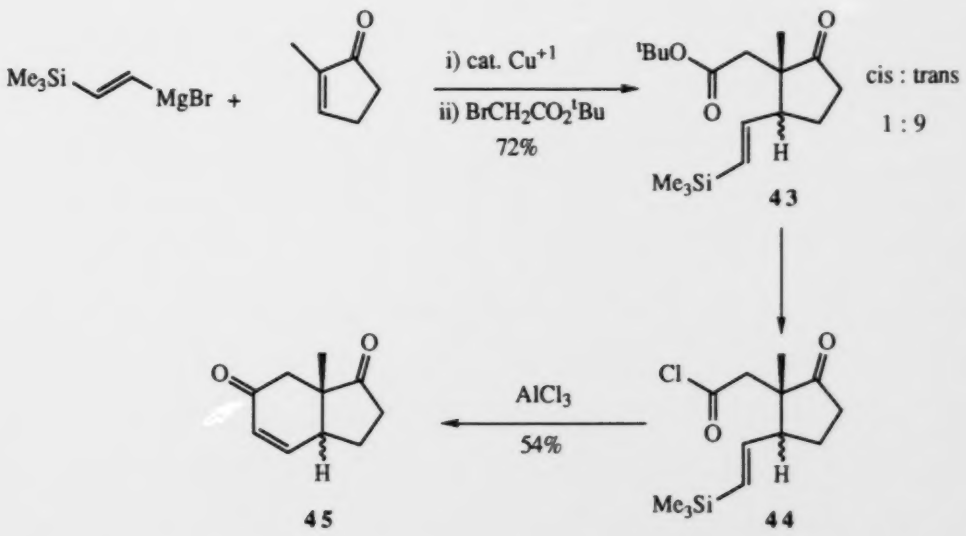
The two pendants can be attached to an existing ring in one reaction by capturing, with a suitable electrophile, the regiochemically defined enolate, formed by conjugate addition of an organocuprate to a cyclic α,β-unsaturated ketone (Scheme **17**).[9]

Scheme 17



This three component coupling is attractive in view of its directness and synthetic flexibility. For example, conjugate addition of the vinyl silane (Scheme **18**) to methyl cyclopentenone and alkylation with *t*-butyl bromoacetate gave a 9:1 mixture (*trans*:*cis*) of ketone **43**. Conversion of the

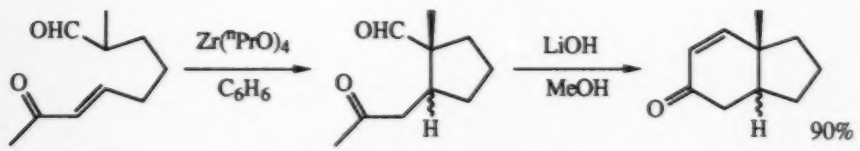
Scheme 18



ester into the corresponding acid chloride **44** followed by vinyl-silane acylation afforded the diketone **45** in 54% yield.[9a]

Stork has described the preparation of *trans* hydrindanes utilizing intramolecular Michael additions[10a-f] to obtain the cyclopentanes **47**, which are set up to undergo aldol condensation. The success of this approach depends upon the stereoselectivity of the internal Michael reaction. He has found that the selectivity is strongly dependent on the conditions used to catalyze the reaction, and best results were obtained using zirconium *n*-propoxide (*cis*:*trans* = 1:40).

Scheme 19



46 **47** **48**

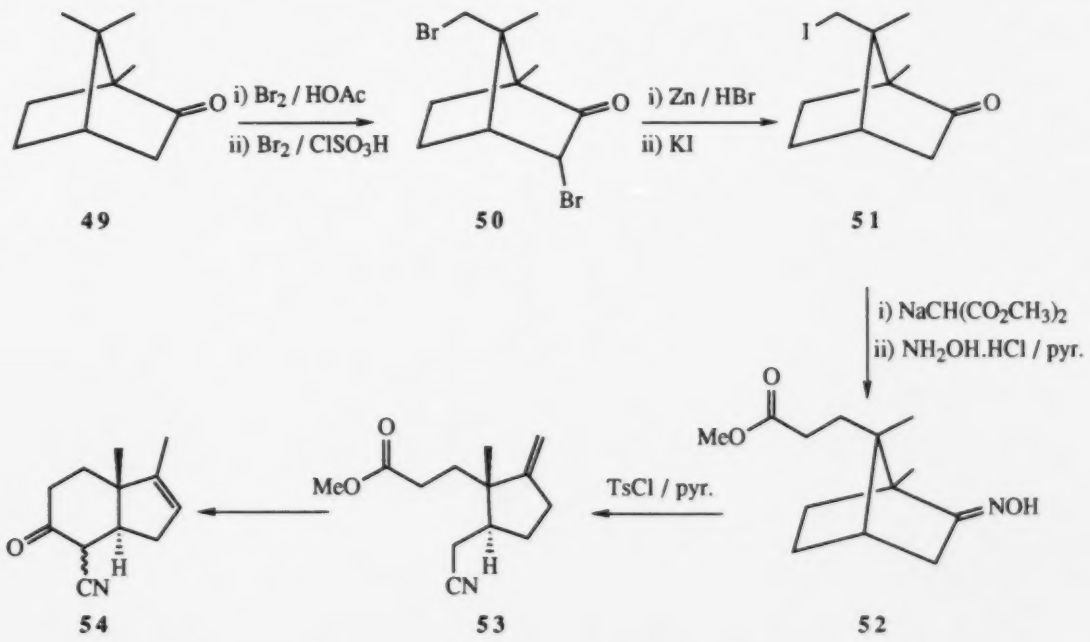
cis : trans
1 : 40

Aldol condensation and elimination gave a 90% yield of the enone **48**. Fallis[10g] and Yamamoto[10h] have published similar results.

The fragmentation of bicycloheptanes to produce *trans* substituted cyclopentanes is an attractive route for the preparation of hydrindanes.[11] For example, Stevens[11a] has brominated (-)-camphor **49** to give the bis halide **50**. The

bromine at the α-keto position was removed, and exchange of the bromine at C-9 with potassium iodide gave 9-iodocamphor. The neopentyl iodide was displaced with dimethylmalonate and the oxime was then prepared from the ketone. Treatment of the oxime with tosyl chloride and pyridine resulted in fragmentation to give the substituted cyclopentene **53**. Isomerization of the exocyclic double bond, and Dieckmann-like condensation resulted in a ~30% yield (from 9-iodocamphor) of the *trans* hydrindane **54**.

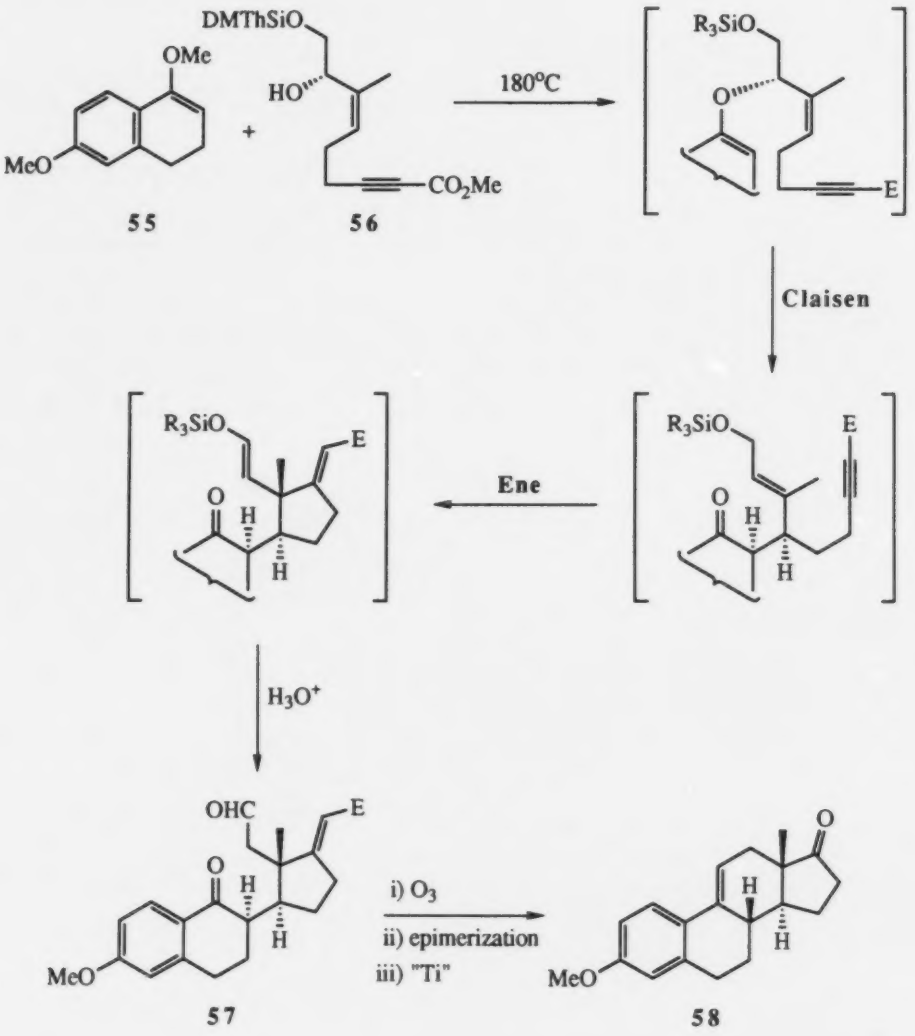
Scheme 20



Nakai[12a] has reported an interesting asymmetric tandem Claisen-ene Strategy (Scheme **21**) for the synthesis of the CD

ring portion of a steroid. A solution of alcohol **56** and the vinyl ether **55** were heated in a sealed tube at 180°C. Transetherification was followed in situ by a Claisen-ene

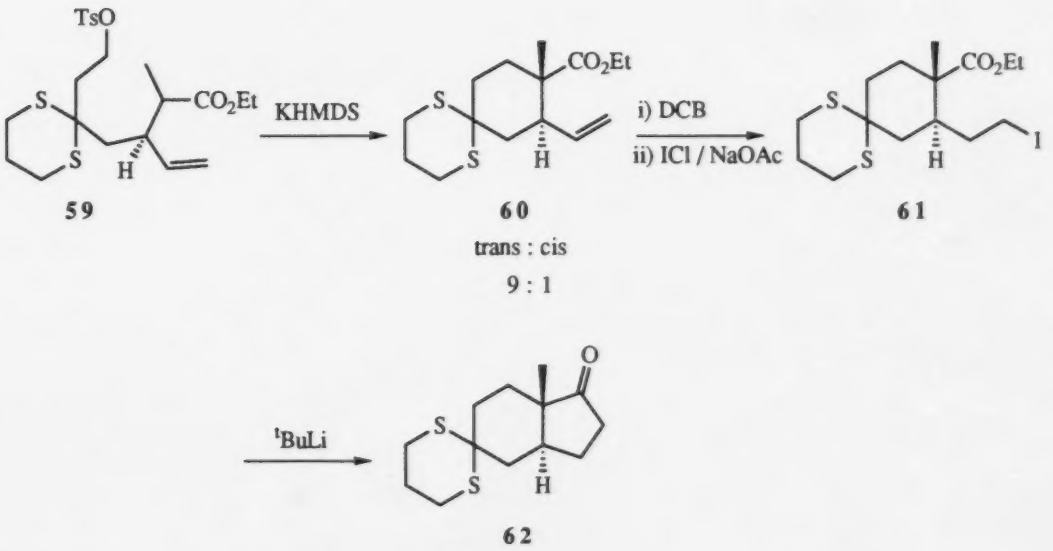
Scheme 21



sequence, and the substituted cyclopentane **57** was isolated in 76% yield. Ozonolysis of the exocyclic vinyl ester and McMurry coupling of the keto aldehyde provided easy access to a steroid intermediate **58**.

Finally, Kim[12b,c] has published a stereoselective method for construction of a steroidal *trans* hydrindane synthon. The procedure is based upon an intramolecular ester enolate alkylation (Scheme **22**). The key vinyl ester **60** was obtained

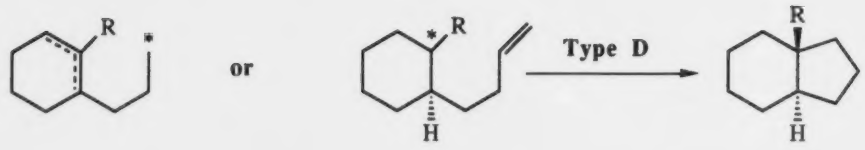
Scheme 22



in 82% yield, as a 9:1 (*trans:cis*) mixture, upon cyclization of the tosylate **59**. Hydroboration of the olefin, followed by anionic cyclization of the primary iodide **61**, gave the *trans* hydrindanone **62**.

Type D Approaches

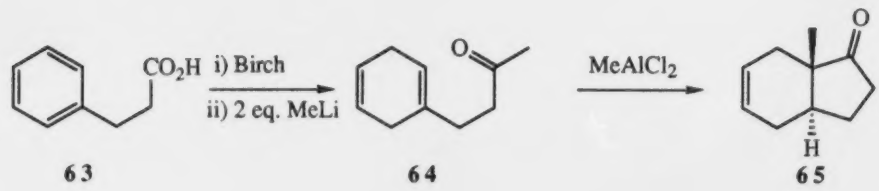
Scheme 23



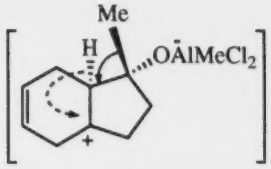
The last general strategy for the construction of *trans* hydrindanes is that of Type D. In these examples the *trans* stereochemistry is determined at the stage of bond formation to a ring junction atom.

Snider[13a] has investigated the Lewis acid initiated cyclization of the keto-olefin **64**. This compound is readily obtained (Scheme **24**) in two steps from hydrocinnamic acid **63**. The *trans* hydrindane was obtained in 50% yield upon heating a dichloromethane solution of **64** in a sealed tube with $MeAlCl_2$.

Scheme 24



The reasons for the stereochemical outcome of the reaction are not completely understood; however, it is tempting to suggest concerted hydride and methyl shifts, as in **66**.

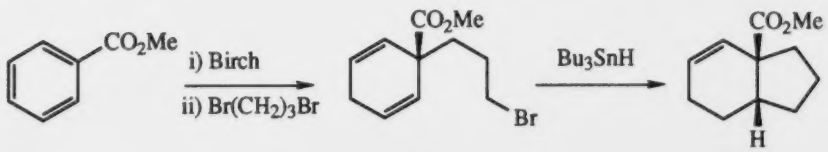


66

The rather harsh conditions of the reaction limit its generality and may preclude its application to more highly functionalized systems.

The use of free radical chemistry to form a bond to a ring junction atom in hydrindanes usually results in the formation of the *cis* isomer.[13b] The work of Beckwith[13c] (Scheme **25**) is typical of the stereochemical results one can expect in the cyclization of 5-hexenyl radicals. Reductive alkylation of the benzoic acid ester **67** provided bromide **68**. Tributyltin hydride mediated cyclization gave an 88% yield of the *cis* fused indane derivative **69**.

Scheme 25

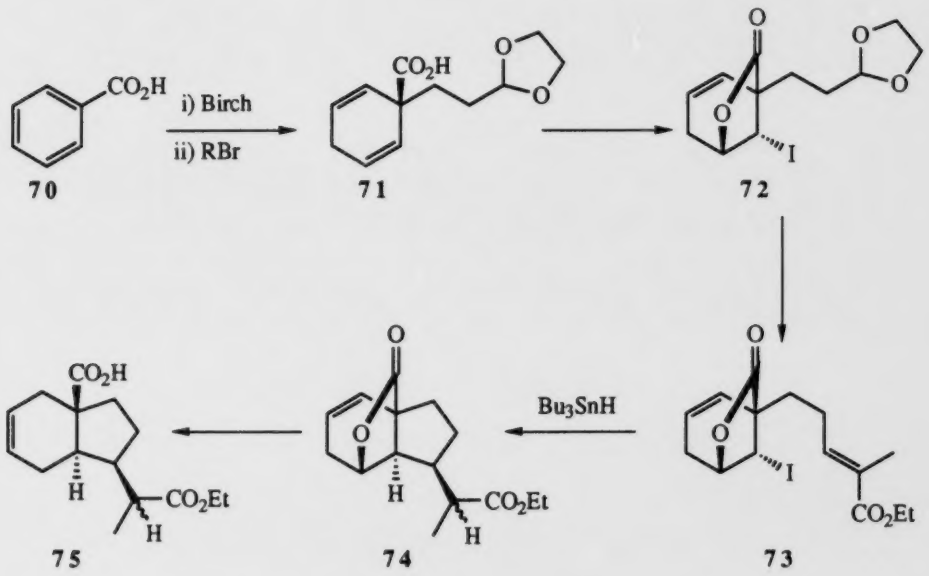


67 **68** **69**

Hart[13d] has developed a modification of Beckwith's reductive alkylation sequence, which leads to a *trans* ring fused hydrindane system (Scheme **26**). Alkylation of the Birch

reduction product with the protected bromo-aldehyde gave acid **71**. Iodolactonization of the acid served two important purposes: it provided the radical source and it also determined the ring fusion geometry for the cyclization step. The aldehyde was deprotected and converted (via Horner-Emmons chemistry) to the unsaturated ester **73**. 5-*Exo* cyclization provided the tricyclic lactone **74** in which the newly formed 5,5 bicyclic system has *cis* ring fusion. In the process, a *trans* ring fused hydrindane has been formed. After appropriate functional group modifications, reductive cleavage of the lactone provided the *trans* hydrindane **75**.

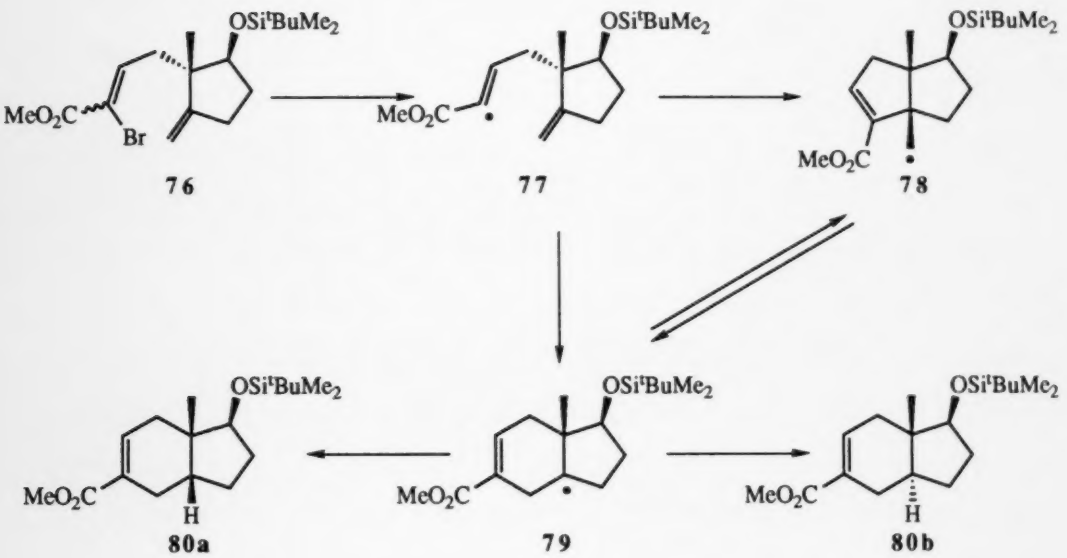
Scheme 26



Hart has used this methodology in the synthesis of pleurotin, an antitumour antibiotic.[13e]

Another approach (Scheme **27**) to *trans* hydrindanes, in which the stereochemistry of the ring junction is set up in a radical cyclization step, is described by Shibasaki.[13f] Cyclization of vinyl radicals of type **77**, under conditions which allow rearrangement of kinetically controlled products **78**, afford the secondary radicals **79**, which then abstract a hydrogen atom. The stereochemistry of the resultant hydrindane is determined in the hydrogen abstraction step and

Scheme 27



reflects the relative stability of the transition states leading to the *cis* (**80a**) or *trans* hydrindane (**80b**). The transition state energy is determined, at least in part, by the ease of access of stannane to either face of the bicyclic radical intermediate. The *trans* angularly methylated

hydrindane **80b** was obtained in a highly stereoselective manner (*trans:cis* = 95:5) in 87% yield.

Conclusions

It is obvious from the above discussion that the challenge of constructing *trans* hydrindanes in a stereocontrolled manner has resulted in the development of several new and ingenious protocols. It is to be expected, however, that much further research will be reported in an effort to obtain simple and general methods that work with exceptionally high levels of stereoselectivity and which also give optically pure products.

II. DISCUSSION*

Background

The ring fusion stereochemistry of bicyclic compounds prepared by 5-*exo* radical cyclization of the type shown in Scheme **28** can be predicted.[13b, 14] For values of n = 1 or 2

Scheme 28

81 **82**

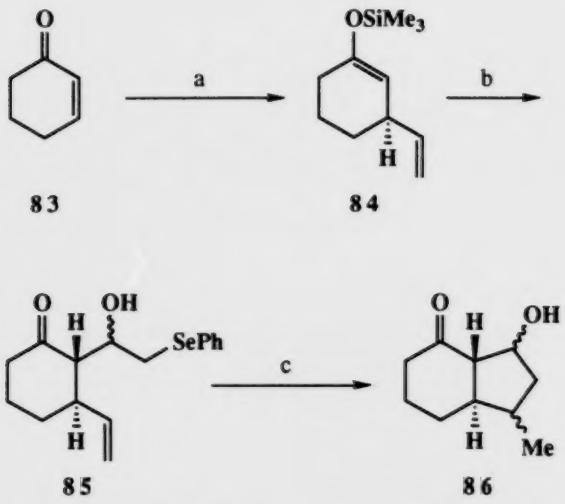
radical ring closure under conditions of kinetic control gives products with *cis* ring fusion. Both *cis*- and *trans*-ring fused carbocycles are produced in cyclizations forming 5,7 bicyclic compounds (i.e. n = 3). Therefore, *trans*-ring fused compounds are best prepared by radical reactions in which the last bond to be made in the ring forming process is <u>not</u> a bond to one of the ring junction atoms.[14] This restriction can be accommodated by attaching to a ring a pair of *trans*-disposed substituents, one carrying a radical precursor and the other a suitable radical trap (usually C=C or C≡C).

---

* Some of these results have been published.[15]

A previous approach from our own laboratories,[14] which conforms to these ideas, is illustrated in Scheme **29**. The *trans* disposition of the two pendants is achieved by trapping the regiochemically defined enolate formed by conjugate addition of the organocuprate to cyclohexenone.

Scheme 29



Scheme 29. Reagents and conditions: (a) CH_2=CHMgBr, CuI, TMSCl. (b) MeLi, $PhSeCH_2CHO$. (c) Ph_3SnH, AIBN.

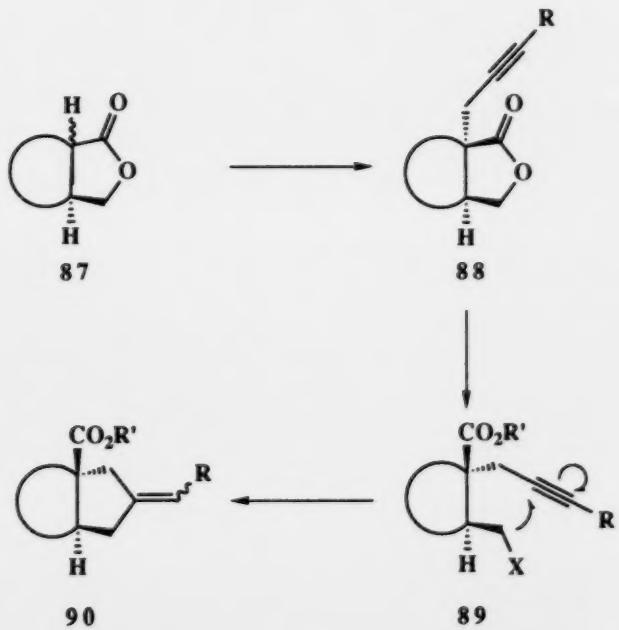
The radical generated from the selenide **85** cyclized by 5-*exo* closure onto the double bond, forming the *trans* hydrindane **86**.

The synthetic utility of radical cyclizations to prepare *trans* fused carbocycles is largely dependent on the ease with which one can assemble precursors for the cyclizations. We were interested in developing additional methodology for the construction of *trans* ring-fused bicyclic compounds.

Consequently we required a method for the placement of two pendants in a *trans* manner on an existing cyclic structure. One pendant would carry a radical precursor and the other pendant a suitable radical trap (C=C or C≡C).

We have developed an alkylation / lactone opening sequence (Scheme **30**) that achieves these goals and leads, after radical cyclization, to *trans* ring-fused compounds.[15] The method relies on the alkylation of fused butyrolactones **87** to give selectively the *cis*-fused product **88** in which the newly introduced alkyl group is syn to the remaining ring fusion hydrogen. This stereochemical result ensures that, after ring opening of the lactone, the pendant carrying the

Scheme 30



radical precursor (CH_2-X) and the unsaturated pendant ($CH_2C{\equiv}CR$) are *trans* to one another. 5-*Exo* cyclization of the radical generated from **89**, provides the bicyclic compounds **90** with *trans* ring-fusion.

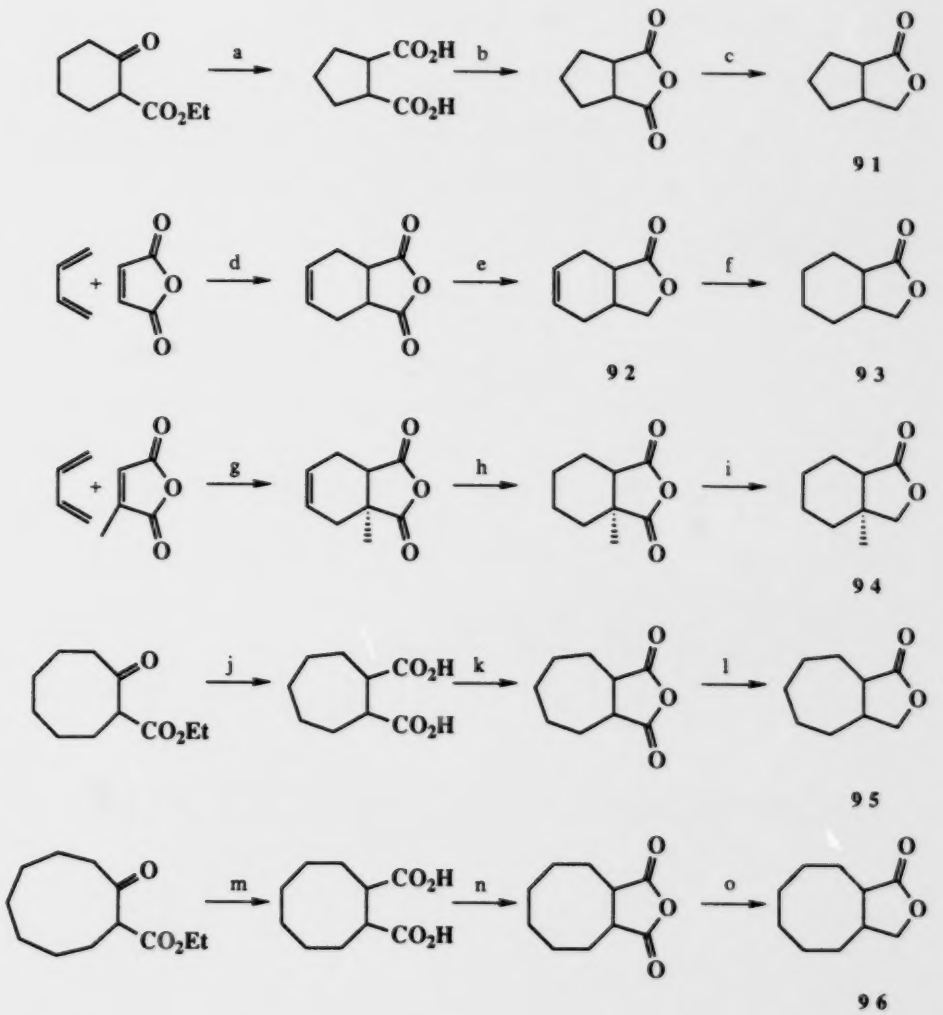
Preliminary experiments done on this sequence, using the lactone **92**, showed the feasibility of such an approach, and the results of these examples will be discussed for completeness, although the experimental details are reported elsewhere.[15b] My own work involved the following: (a) elaboration of the method to other ring sizes, (b) demonstration that the cyclized products are amenable to further modification, and (c) proving the stereochemistry of the initial alkylation process.

Scope and Limitations

The starting lactones are easily prepared by a number of convenient routes. They are available in enantiomerically pure form by enzymatic oxidation of monocyclic meso diols[16a] or they can be made by radical cyclization of acyl radicals.[16b] The most general preparation however is by partial reduction of anhydrides using sodium borohydride[16c] or lithium aluminum hydride.[16d] The anhydrides required for these reductions were obtained as shown in Table **2**. The anhydrides fused to five-, seven-, and eight-membered carbocycles were prepared by a Favorski rearrangement-dehydration sequence.[17] Anhydrides fused to a six-membered carbocycle were conveniently prepared by Diels-Alder reaction

of appropriately substituted maleic anhydrides with butadiene.[16d]

Table 2



Footnotes to Table 2: (a) Br_2, KOH; 65%. (b) Ac_2O; 58% (77% BOC). (c) $NaBH_4$, H_3O^+; 78%. (d) Δ; 80%. (e) $LiAlH_4$, H_3O^+; 67%. (f) Pd/C, H_2; 98%. (g) Δ. (h) Pd/C, H_2; 100%. (i) $LiAlH_4$, H_3O^+; 72%. (j) Br_2, KOH; 69%. (k) Ac_2O; 99%. (l) $NaBH_4$, H_3O^+; 76%. (m) Br_2, KOH. (n) Ac_2O; 83% from keto-ester. (o) $NaBH_4$, H_3O^+; 74%.

We next examined alkylation of the lactones. It should be emphasized that this is the key step of the sequence because it is at this stage that the ring fusion stereochemistry of the final cyclized products is determined. In the cases we have examined (Table **3**) the unsaturated chain in the alkylated product is syn to the remaining ring fusion hydrogen.[18] In the alkylation, the electrophile (containing the unsaturated pendant) can approach the endocyclic enolate from either face of the five membered ring lactone (Scheme **31**). Approach of the electrophile from the bottom face suffers from steric interaction with the methylene of the

Scheme 31

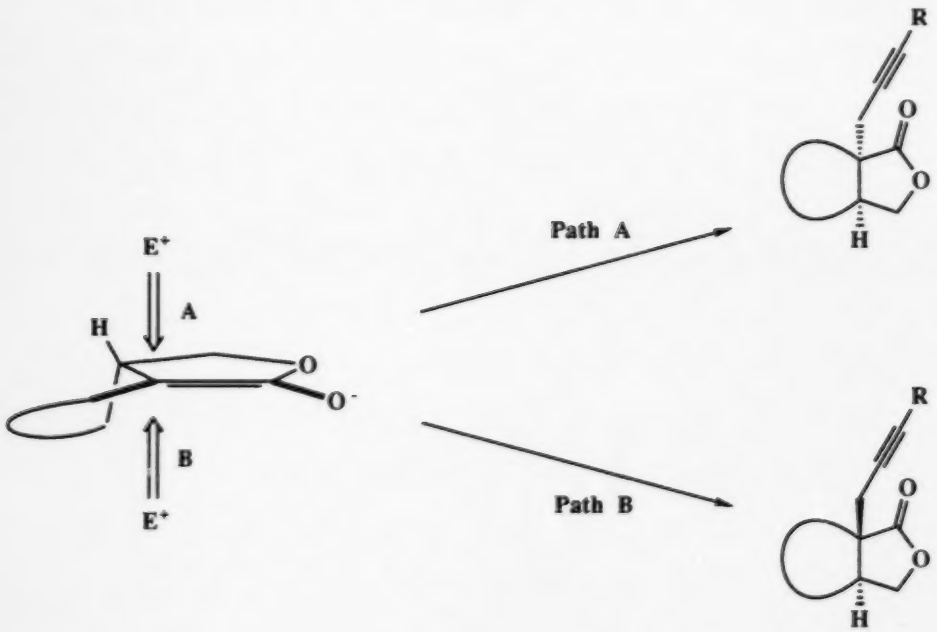


TABLE 3

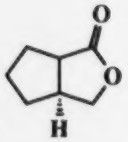
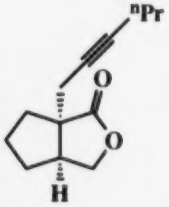
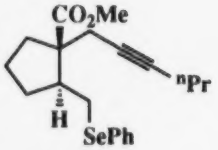
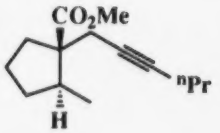
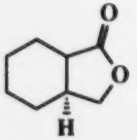
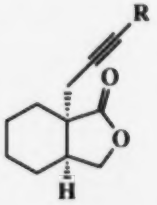
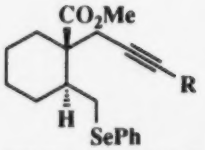
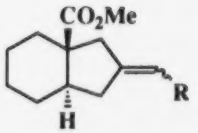
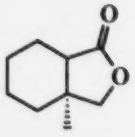
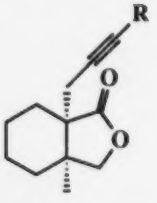
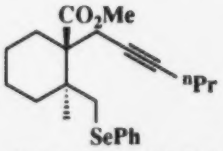
Lactone	Alkylated Lactone	Selenide	Cyclized Product
			
91	**97** (63%)	**98** (81%)	**99** (~14%)
			
93	**100 R = Ph** (97%) **101 R = ^{n}Pr** (88%)	**102 R = Ph** (72%; 100% BOC) **103 R = ^{n}Pr** (77%; 87% BOC)	**104 R = Ph** (96%) **105 R = ^{n}Pr** (82%)
			----[a]
94	**106 R = Ph** (90%) **107 R = ^{n}Pr** (90%)	**109 R = ^{n}Pr** (14%; 79% BOC)	

TABLE 3 (cont.)

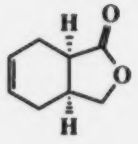
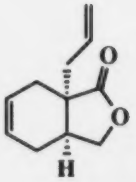
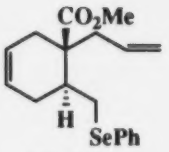
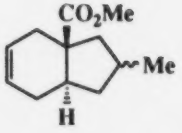
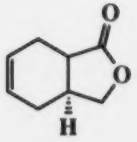
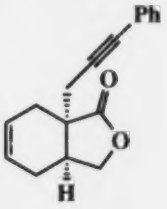
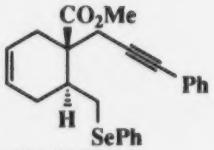
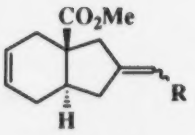
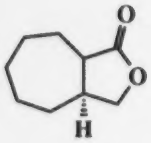
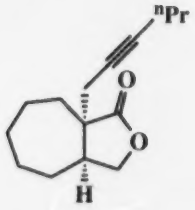
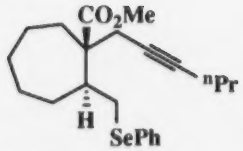
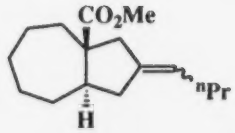
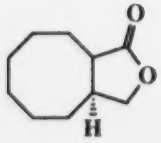
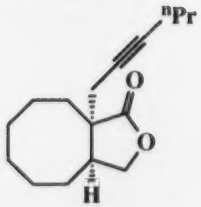
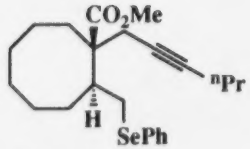
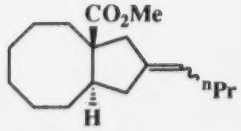
Lactone	Alkylated Lactone	Selenide	Cyclized Product
			
92	**110** (89%)	**111** (74%)	**112** (92%)
			
92	**113** (95%)	**114** (83%)	**115 R = Ph** (73%)

TABLE 3 (cont.)

Lactone	Alkylated Lactone	Selenide	Cyclized Product
			
95	**116** (89%)	**117** (66%; 86% BOC)	**118** (79%[b]; 95%[c])
			
96	**119** (72%)	**120** (74%)	**121** (77%[b]; 87%[c])

Footnotes to Table 3: (a) Experiment not tried; (b) Ph_3SnH / AIBN used for radical cyclization; (c) Ph_3SnH / Et_3B used for radical cyclization.

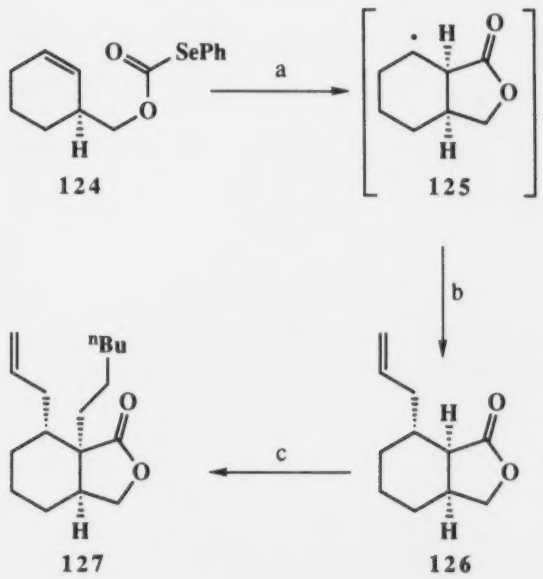
chain which forms part of the fused carbocycle. Approach of the electrophile syn to the ring fusion hydrogen (Path **A** in Scheme **31**) does not suffer from this interaction.

Our initial alkylation studies used **122** ($PhC{\equiv}CCH_2Br$); however it became necessary to purify the alkylating agent before each use due to slow decomposition. The propargyl bromide **123** ($^nPrC{\equiv}CCH_2Br$) was used in subsequent experiments and proved to be equally effective. The aliphatic bromide **123** offered the advantage that it could be stored at -5°C for extended periods without noticeable decomposition. The purpose of using an acetylene instead of an allyl compound in the alkylation step lies in the fact that with an acetylene the resulting cyclized product retains a synthetically useful double bond. This does not mean that the unsaturated pendant is limited to an acetylene, as lactone **92** was also alkylated efficiently with allyl bromide. Alkylation yields ranged from 63 to 97% and only in one case (**116**) was a small amount (about 0.6% yield) of the *trans* isomer isolated. The crude alkylation mixtures were not examined spectroscopically, therefore we can not be absolutely certain that *trans* isomers were not formed in the other examples. However, no other products were visible by thin layer chromatography.

We have shown that alkylation occurs in the desired stereochemical sense when the ring fusion hydrogen is replaced by a methyl group (as in **94**). We have also demonstrated that alkylation still occurs in the desired stereochemical sense when a substituent is present adjacent

to the alkylation site, as in **126**. This compound was prepared by acyl radical cyclization[16b] and intermolecular addition,[19] as outlined in Scheme **32**.

Scheme 32



Scheme 32. Reagents and conditions: (a) $(Bu_3Sn)_2$, *hν*. (b) CH_2=$CHCH_2SnBu_3$; 72% from **124** (c) LDA, $C_6H_{13}Br$; 80%.

The acyl radical was generated photolytically from the selenocarbonate **124** in the presence of an excess of allyltributyltin. 5-*Exo* cyclization provides the secondary radical **125** which adds to allyltributyltin giving the *cis* fused lactone **126**. A tributyltin radical which carries on the chain reaction is released at the same time. The lactone **126** was alkylated with 1-bromohexane to provide **127** in which the newly introduced alkyl group is *syn* to the remaining ring fusion hydrogen. In this experiment it was not necessary to

use an unsaturated electrophile as we were interested only in the stereochemistry of alkylation - not in the radical step.

The alkylated lactones were cleaved with sodium phenylselenide using the standard literature procedure.[20] The crude reaction products were treated with an excess of ethereal diazomethane to convert the the resulting acids to their methyl esters. It was sometimes difficult to drive the ring opening reaction to completion and in such experiments recovered lactone was isolated. In the case of lactone **107**, we could not obtain synthetically useful yields of the ring opened product, which requires S_N2 displacement by sodium phenylselenide at a neopentyl center. With added catalyst (18-crown-6)[20b] and prolonged heating (~4 days) a low yield of the desired selenide **109** was obtained along with unreacted starting material.

The final step of the sequence involves generation of the radical from the selenide by reaction with stannane[21] and conventional 5-*exo* closure. The radical reaction could be initiated thermally by simultaneous addition of benzene solutions of triphenyltin hydride and azoisobutyronitrile to a benzene solution of the selenide at reflux.[21a] A more convenient procedure[21b] involves the addition of triethylborane to a stirred solution of the selenide and triphenyltin hydride in hexane at room temperature. Initiation occurs chemically by the reaction of triethylborane with dissolved oxygen.[21c] Higher yields were

$$Et_3B + O_2 \longrightarrow Et_2B\text{-}O\text{-}O^{\cdot} + Et^{\cdot}$$

$$R_3SnH + Et^{\cdot} \longrightarrow R_3Sn^{\cdot} + C_2H_6$$

generally obtained using the later procedure.

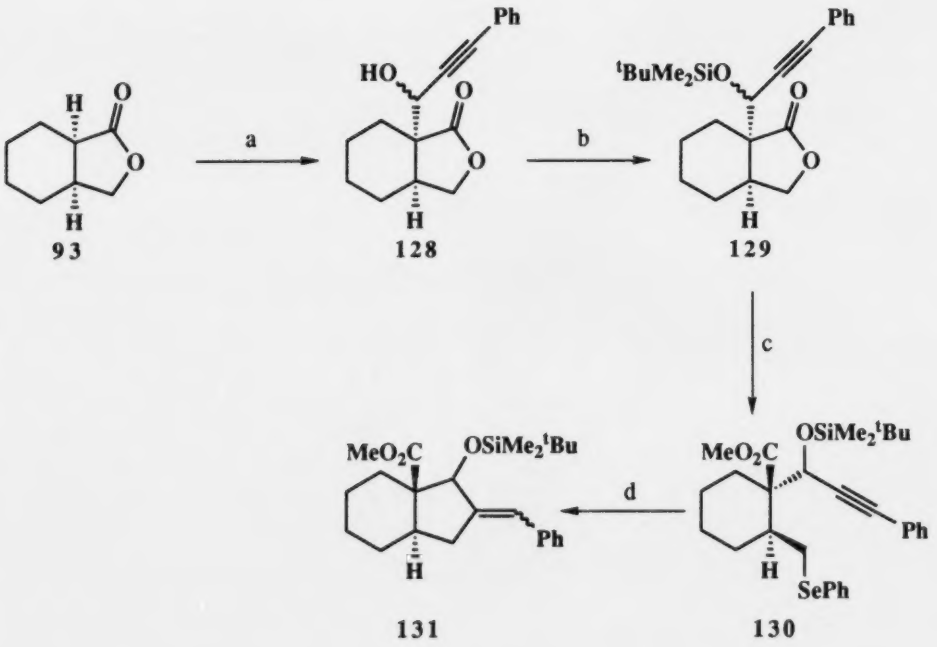
The present method is suitable for constructing *trans* ring-fused 5,6-, 5,7-, and 5,8-systems. The cyclized products were obtained in excellent yields (73-96%) as mixtures of *Z*- and *E*-isomers.

Radical cyclization of olefin **111** was highly efficient (92%) and yielded the saturated cyclized compound **112** as a mixture of isomers in a 13.5:1 ratio. We did not see products resulting from cyclization onto the double bond of the six membered ring.[21d]

Attempted preparation of *trans* 5,5-bicyclic system by this method failed and we obtained a low yield (14%) of the noncyclized reduction product **99**. This result was not surprising in light of the strain inherent in a *trans* 5,5-bicyclic system.[22]

The unsaturated pendant can be introduced by aldol condensation instead of alkylation (Scheme **33**). Treatment of the enolate prepared from lactone **93** with phenylpropargyl aldehyde, gave **128** as an equimolar mixture of diastereoisomers. The hydroxyl group must be protected before the lactone ring is cleaved, as attempted ring opening at the alcohol stage resulted in regeneration of the lactone **93** by reverse aldol reaction.

Scheme 33



93 128 129 131 130

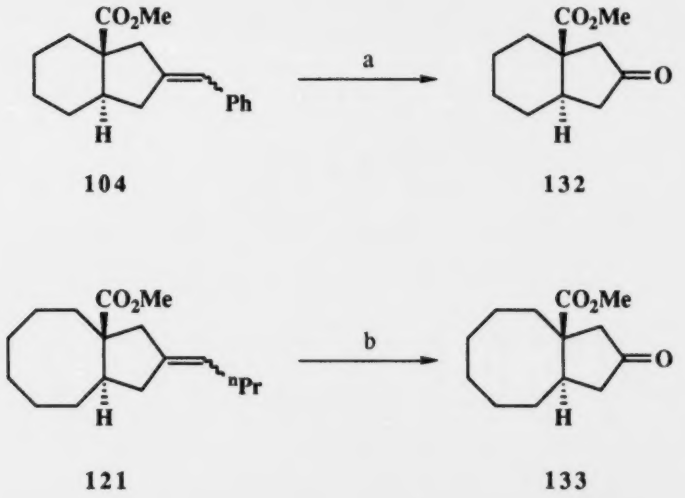
Scheme 33. Reagents and conditions: (a) LDA, PhC≡CCHO; 95%. (b) TBDMSCl, Et_3N, DMAP; 85%. (c) chromatography over SiO_2; PhSeNa, then CH_2N_2; 65%. (d) Ph_3SnH, AIBN; 78%.

After protection of the alcohols as their silyl ethers the two diastereoisomers were separated; however, only one of them was used for the rest of the sequence. Unfortunately, it was not possible to make any stereochemical assignments on either of the diastereoisomers. The lactone ring was cleaved and the selenide **130** was cyclized to give the substituted *trans* hydrindane **131**. This type of aldol process is attractive because it allows regiochemical differentiation between the methylene positions on either side of the exocyclic double bond.

Functional Group Modification

The acetylenes were chosen as the radical trap in the cyclization reactions because the olefins produced would be amenable to further modification. In this context we

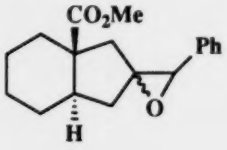
Scheme 34



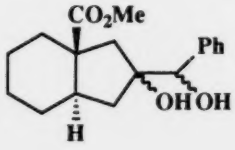
Scheme 34. Reagents and conditions: (a) O_3, MeOH, CH_2Cl_2, then Ph_3P; 64%. (b) O_3, MeOH, CH_2Cl_2, then Ph_3P; 82%.

examined oxidative cleavage of the exocyclic double bonds (Scheme **34**) in compounds **104** and **121**. Ozonolysis, followed by a reductive work-up, provided the ketones **132** and **133** in 73 and 82% yield, respectively. We also examined the periodate cleavage of epoxides **134**[23] and diols **135**,[24] however, the results were less promising. A large number of naturally occurring bicyclic systems contain a methyl

group at the angular position, and so we have shown that the angular ester group can easily be reduced to a methyl group.



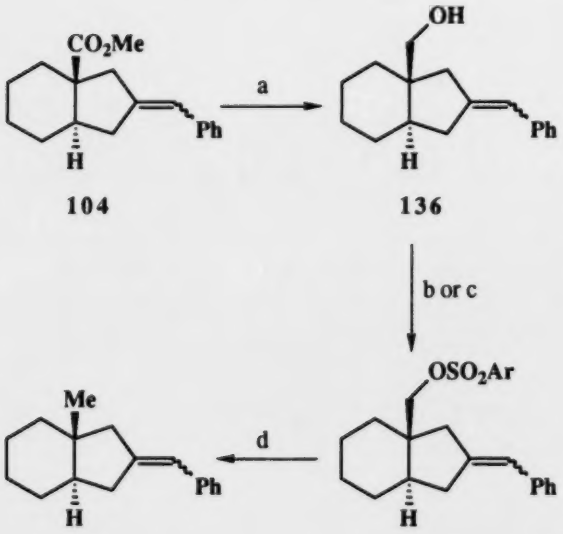
134



135

Reduction of the esters **104** provided (Scheme **35**) the alcohols **136** in quantitative yield, and the corresponding

Scheme 35



104 **136** **139**

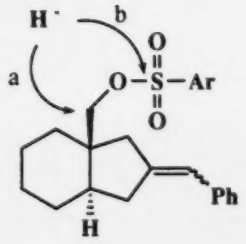
137 Ar = *p*-Tol
138 Ar = 2,4,6-Triisopropylbenzene

Scheme 35. Reagents and conditions: (a) $LiAlH_4$; 95%. (b) TsCl, pyridine; (**137**) 100%. (c) 2,4,6-(^{i}Pr)$_3C_6H_2SO_2Cl$, pyridine; (**138**) 81%. (d) $LiEt_3BH$; 56%(from **137**); 94%(from **138**).

tosylates **137** were then prepared. Hydride displacement of the tosylates with excess lithium triethylborohydride[25] afforded the desired reduced compounds **139** in 56% yield, along with significant amounts (42%) of recovered alcohol **136**.

If, however, the more sterically demanding triisopropylbenzenesulphonates **138** are prepared, and reduced with excess Superhydride, the desired reduction products **139** are obtained in nearly quantitative yield.

There are two possible mechanisms for the reduction of alkylsulphonates. It is tempting to explain the above results as arising by a direct hydride displacement mechanism. Treatment of the tosylates **137** with Superhydride suffers from competitive displacement (see **140**) at the hindered neopentyl position (a) and hydride addition to the sulfonate (b).

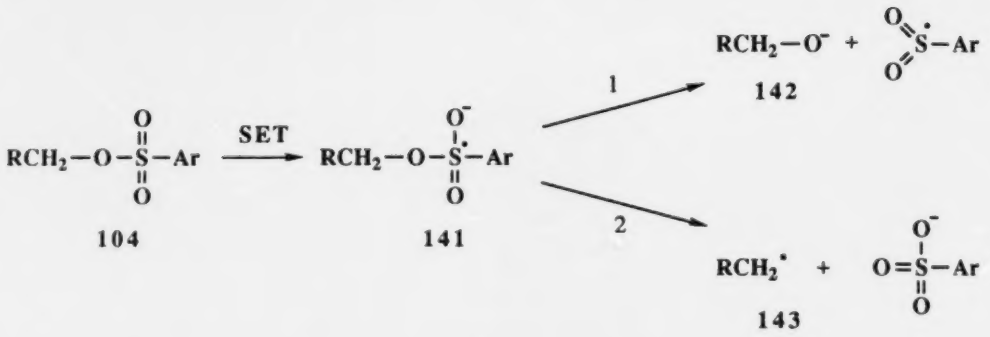


140

In the triisopropylbenzenesulfonate example, the increased steric bulk around the sulfonate favors the direct displacement at the neopentyl position. However, an

alternative mechanism is a single electron transfer (SET) process[26] (Scheme **36**).

Scheme 36



SET from the hydride reducing reagent would give the ketyl-like radical **141**, which can undergoes two possible reactions: (1) β-elimination of alkoxide **142** to form alcohol **136** or (2) β-fragmentation of an alkyl radical **143** which then leads to reduced product **139**. Unfortunately, with the information available we cannot differentiate between the mechanisms, and a detailed study is beyond the scope of our work.

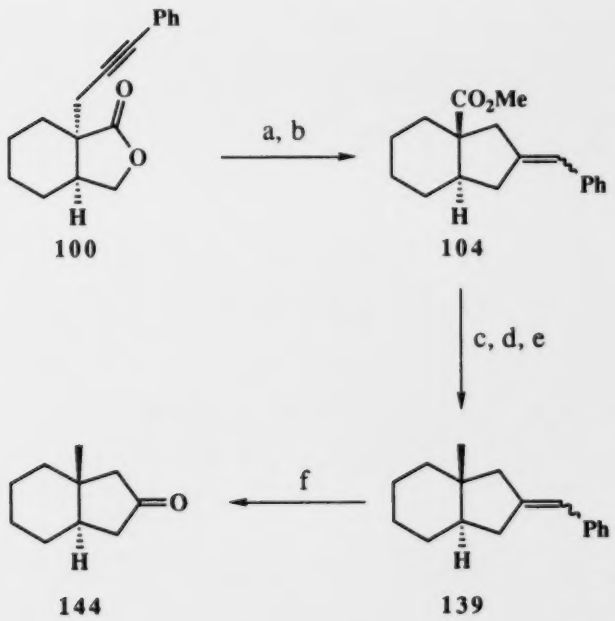
Stereochemical Assignment

It was necessary in this work to prove the stereochemistry of the initial alkylation products. Nuclear Overhauser experiments done on **107** (page 122) and **116** (page 124) were not conclusive. We had attempted to use nOe to prove the syn relationship between the ring junction hydrogen

and the methylene hydrogens next to the acetylene; however we were not confident with the results.

The alkylated lactone **97** (page 122) was assumed to be *cis* fused due to the high strain energy of a *trans* 5,5 bicyclic system. This assumption is supported by the fact that attempted cyclization of the selenide **98** (page 122) failed and reduced non-cyclized product was isolated instead.

Scheme 37



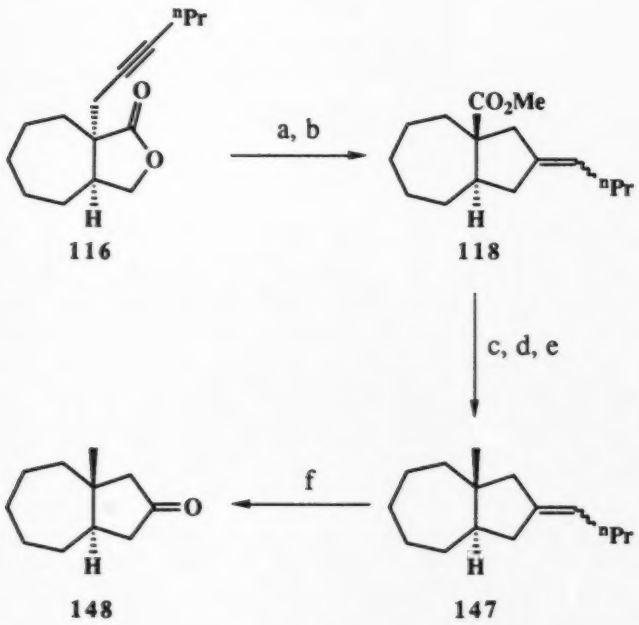
Scheme 37. Reagents and conditions: (a) PhSeNa / CH_2N_2; 72%. (b) Ph_3SnH, AIBN; 96%. (c) $LiAlH_4$; 95%. (d) 2,4,6-(^{i}Pr)$_3C_6H_2SO_2Cl$, pyridine; 81%. (e) $LiEt_3BH$; 94%. (f) O_3, MeOH, CH_2Cl_2, then Ph_3P; 60%.

The stereochemistry of the 6,5-alkylated lactone **100** was proven by conversion to the bicyclic ester **104**. The ester was reduced and the olefin was cleaved (Scheme **37**) to provide

the angularly methylated *trans* hydrindanone **144**, which was spectroscopically distinguishable (^{13}C NMR) from the corresponding *cis* isomer which is a known compound.[27]

The stereochemistry of the alkylated lactone **116** was proven in the same way. The cyclization product was degraded as before (Scheme **38**) to the *trans* ketone **148** which is a known compound.[28]

Scheme 38

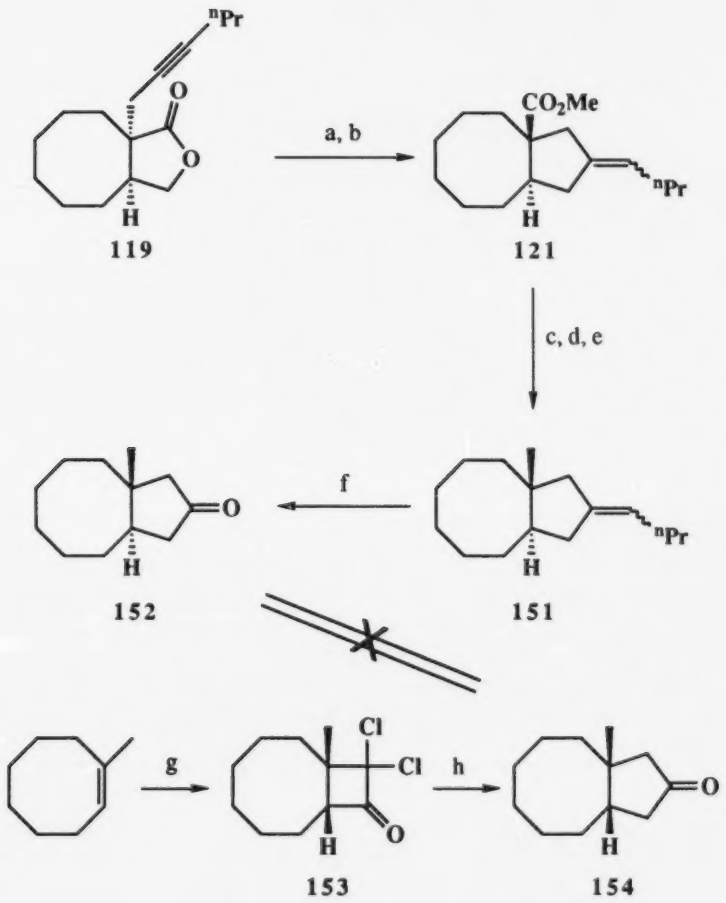


Scheme 38. Reagents and conditions: (a) PhSeNa / CH_2N_2; 66%. (b) Ph_3SnH, Et_3B; 95%. (c) $LiAlH_4$; 99%. (d) 2,4,6-(^{i}Pr)$_3C_6H_2SO_2Cl$, pyridine; 76%. (e) $LiEt_3BH$; 73%. (f) O_3, MeOH, CH_2Cl_2, then Ph_3P; 50%.

The stereochemistry of the alkylated lactone **119** was also determined by this method. The cyclized product was degraded to ketone **152** and found to be different from the

corresponding *cis* ketone **154**, which was prepared[29] as outlined in Scheme **39**.

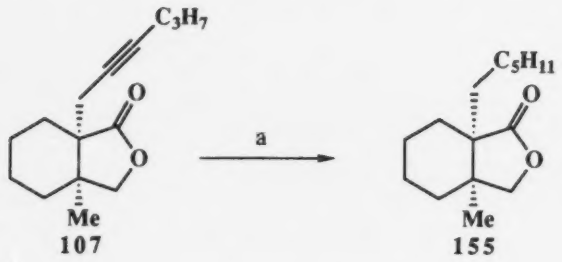
Scheme 39



Scheme 39. Reagents and conditions: (a) PhSeNa / CH_2N_2; 74%. (b) Ph_3SnH, Et_3B; 87%. (c) $LiAlH_4$; 100%. (d) TsCl, pyridine. (e) $LiEt_3BH$; 9%. (f) O_3, MeOH, CH_2Cl_2, then Ph_3P; 65%. (g) $O{=}C{=}CCl_2$; 38%. (h) CH_2N_2, Zn, HCl; 28%.

The stereochemistry of alkylated lactone **107**, in which the ring fusion hydrogen has been replaced by a methyl group, was determined as follows: The triple bond was completely

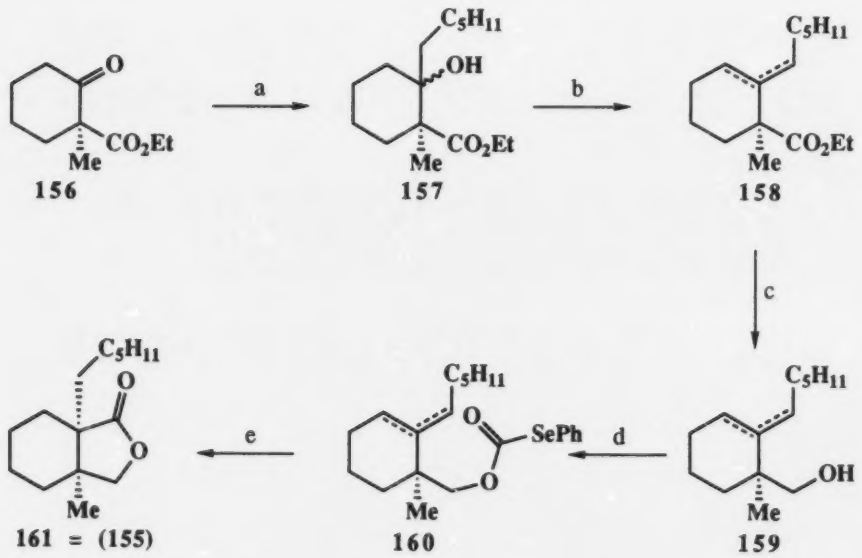
Scheme 40



Scheme 40. Reagents and conditions: (a) H_2, Pd/C; 96%.

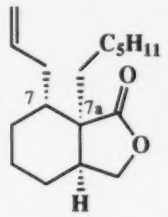
hydrogenated to provide the saturated analogue **155**. This compound was found to be spectroscopically identical to **161**,

Scheme 41



Scheme 41. Reagents and conditions: (a) $C_6H_{13}MgBr$; 57%. (b) Δ, (-H_2O). (c) $LiAlH_4$; 88% from **157**. (d) $COCl_2$; PhSeH; 93%. (e) Ph_3SnH, Et_3B; 92%.

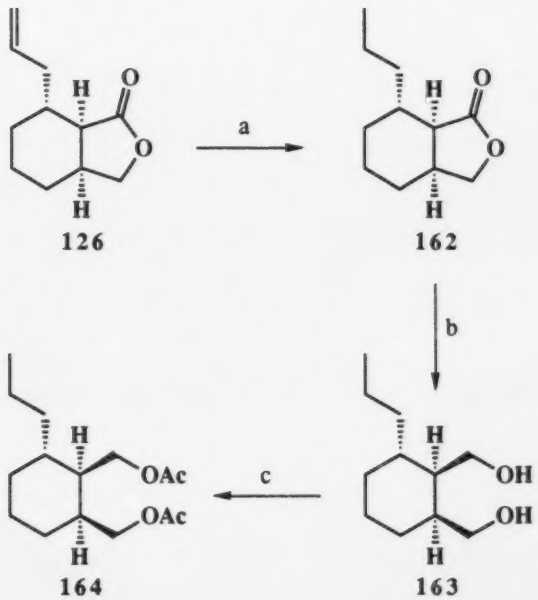
itself prepared (Scheme **41**) by radical cyclization[16b] (**160→161**), a process known[14] to generate *cis* fused products.



127

Lactone **127** has two centers whose stereochemistry had to be determined, C-7 and C-7a. The stereochemistry at 7 is

Scheme 42

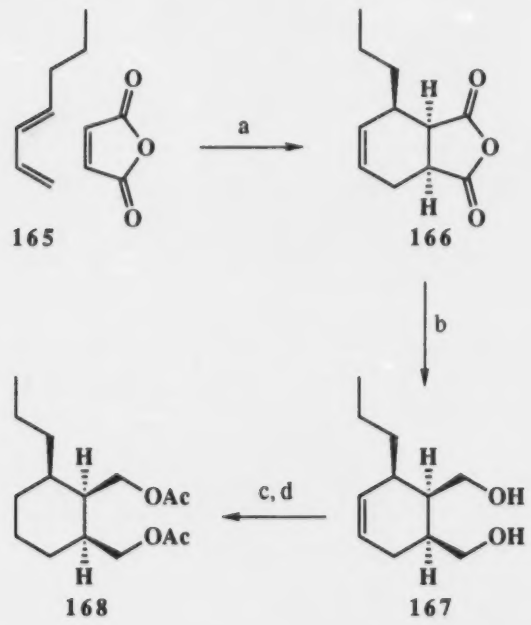


126 **162** **164** **163**

Scheme 42. Reagents and conditions: (a) H_2, Pd/C. (b) $LiAlH_4$; 83% from **126**. (c) Ac_2O, pyridine; 89%.

formed at the stage (see Scheme **32**) of radical addition to allyltributyltin. The stereochemistry at 7 was determined by first reduction of the olefin **126** to give the lactone **162**, which was subsequently reduced with lithium aluminum hydride to diol **163**. The diol was derivatised as the diacetate **164** and this compound was compared with an authentic sample prepared as outlined in Scheme **43**. Diels-Alder reaction of diene **165**[30] with maleic anhydride provided **166**, in which the

Scheme 43

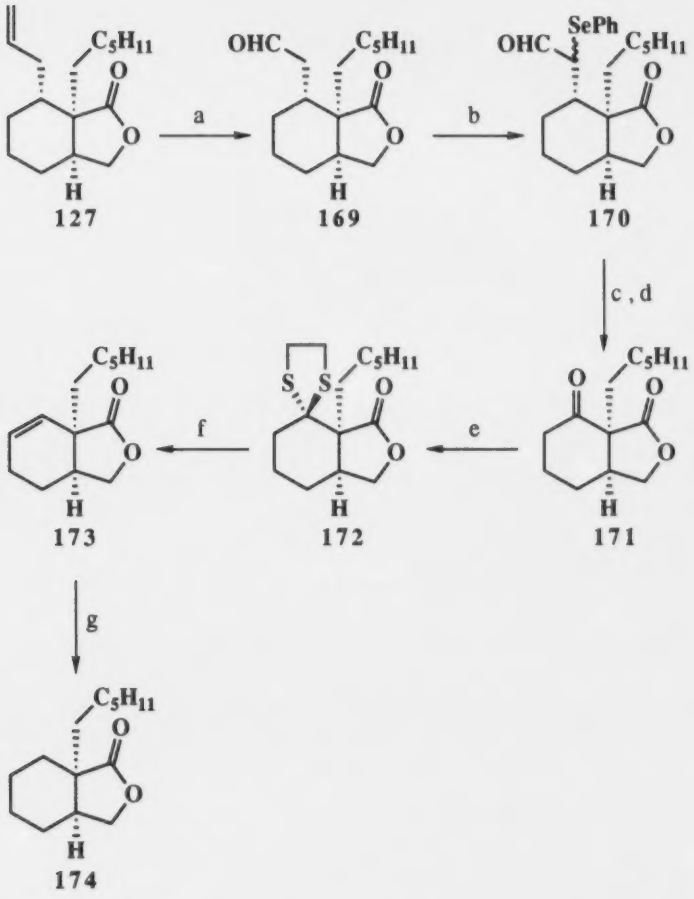


Scheme 43. Reagents and conditions: (a) Δ. (b) $LiAlH_4$; 70% from **165**. (c) Ac_2O; 79%. (d) H_2, Pd/C; 100%.

stereochemistry results from endo addition of the dienophile to the diene. The anhydride **166** was reduced to diol **167** from which was prepared the corresponding diacetate **168**.

Spectroscopic comparison of **164** and **168** showed them to be different and, because the stereochemistry of **168** is determined by Diels-Alder chemistry, the stereochemistry of **164** must be as shown in Scheme **42**.

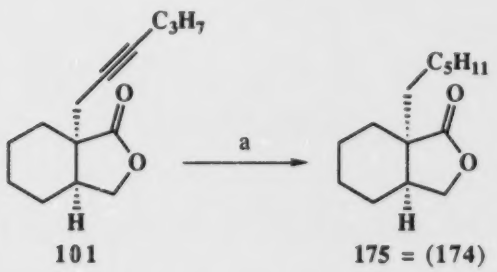
Scheme 44



Scheme 44. Reagents and conditions: (a) O_3, then Ph_3P; 55%. (b) PhSeCl, HCl; 59%. (c) MCPBA. (d) O_3, then Ph_3P; 67% from **170**. (e) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$; 77%. (f) Raney Ni; 73%. (g) H_2, Pd/C; 91%.

The stereochemistry at the angular position (C-7a) was determined as follows: The acyclic chain was oxidatively removed (as outlined in Scheme **44**) to provide ketone **171**. The dithioacetal **172** was prepared and this was desulfurized with Raney nickel to give the olefin **173**. The olefin was hydrogenated over Pd on carbon to provide the saturated lactone **174** and this compound was found to be identical to **175**, prepared by reduction of lactone **101**, whose stereochemistry has already been proven (by analogy to lactone **100**).

Scheme 45



101 **175 = (174)**

Scheme 45. Reagents and conditions: (a) H_2, Pd/C; 77%.

These degradation experiments thus confirm all the stereochemical assignments in those cases where the stereochemistry is not defined by other evidence.

Conclusions

We have demonstrated a general method for construction of *trans* ring-fused carbocycles, suitably functionalized to

permit further modification. Our method is based on an alkylation-lactone ring opening sequence.

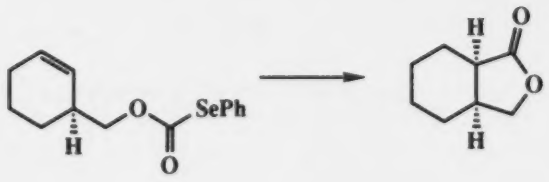
Work is continuing in this laboratory to further develop the methodology.

III. EXPERIMENTAL

The general remarks made in Chapter 1 apply:

General Procedure for Radical Cyclization. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with argon for 5-10 min and benzene was injected into the flask. The flask was placed in an oil bath preheated to 85°C, and solutions of triphenyltin hydride and AIBN in benzene were injected simultaneously via syringe pump over 8 h. Refluxing was continued for an arbitrary period of 2-4 h after the addition. The reaction mixture was cooled and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

***cis*-Hexahydro-1(3*H*)-isobenzofuranone (93).**



124 **93**

Triethylborane (1.0 mL, 1 M in hexane, 1.0 mmol) was added dropwise to a stirred solution of selenide **124** (296 mg, 1.0 mmol) and triphenyltin hydride (527 mg, 1.5 mmol) in hexane (100 mL) (protection from moisture by a drying tube packed with Drierite). The resulting solution was stirred at

room temperature for 24 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 20% ethyl acetate-hexane, gave **93** (129 mg, 92%) as a pure [^{1}H NMR] colorless oil, identical to material prepared by reduction of the corresponding anhydride.[16c,d]

cis-Octahydro-1_H_-cyclohepta[c]furan-1-one and _trans_-Octahydro-1_H_-cyclohepta[c]furan-1-one (95).

95

A solution of the *cis*- and *trans*- hexahydro-1*H*-cyclohepta[*c*]furan-1,3-dione[17,31] (980 mg, 5.83 mmol) in THF (2 mL plus 1 mL rinse) was added dropwise (ca 5 min) to a stirred and cooled (0°C) suspension of sodium borohydride (232 mg, 95%, 5.83 mmol) in THF (4 mL). The ice-bath was removed and stirring was continued for 1 h. Hydrochloric acid (3 mL, 6N) and then water (10 mL) were added, and the mixture was extracted with ether (3 x 30 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 15% ethyl acetate-hexane, gave lactone **95** (558 mg, 62%) as a pure [^{1}H NMR] colorless oil and a mixted fraction of the *cis* and *trans* isomers (160 mg) in a 1.3:1 ratio (^{1}H NMR). The following data is for the mixed fraction: FT-IR ($CHCl_3$

cast) 2928, 1771, 1171 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.23-2.47 (m, 11 H), 2.65-2.85 (m, 1 H), 3.71 (dd, J = 10.5, 9.0 Hz, 0.4 H), 3.90 (dd, J = 9.0, 5.0 Hz, 0.6 H), 4.32-4.44 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 26.25, 27.15, 28.13, 28.31, 30.50, 42.47, 45.01, 71.48, 179.69; exact mass, *m/z* calcd for $C_9H_{14}O_2$ 154.0994, found, 154.0996. An analytical sample was prepared by Kugelrohr distillation (100°C, 10 mm Hg). Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.93; H, 9.14.

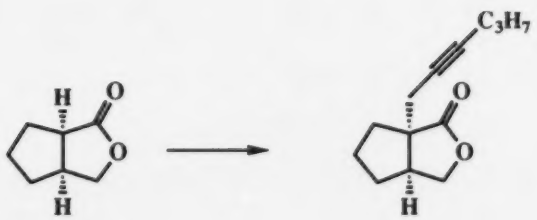
cis-Octahydrocycloocta[c]furan-1(3_H_)-one (96).

96

A solution of the *cis*-hexahydro-1*H*-cycloocta[*c*]furan-1,3-dione[17] (4710 mg, 25.8 mmol) in THF (20 mL) was added dropwise over 10 min to a stirred and cooled (0°C) suspension of sodium borohydride (1.115 g, 95%, 28 mmol) in THF (6 mL). After 1 h the ice-bath was removed and, after a further 2 h the reaction was quenched by cautious addition of hydrochloric acid (11 mL, 6N). The mixture was diluted with water (50 mL) and extracted with ether (3 x 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 18 cm), using 15% ethylacetate-hexane, gave **96** (3234 mg, 74%) as

a pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2920, 1771, 1168, 1040, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.27-1.60 (m, 6 H), 1.63-1.90 (m, 5 H), 2.20-2.45 (m, 3 H), 3.65 (dd, J = 9.5, 9.0 Hz, 1 H), 4.37 (dd, J = 9.0, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 25.21, 25.39, 27.08, 27.28, 30.12, 32.30, 41.64, 44.89, 71.94, 180.40; exact mass, *m/z* calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1149. An analytical sample was prepared by Kugelrohr distillation (130°C, 11 mm Hg). Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.43.

cis-6a-(2-Hexynyl)hexahydro-1_H_-cyclopenta[c]furan-1-one (97).

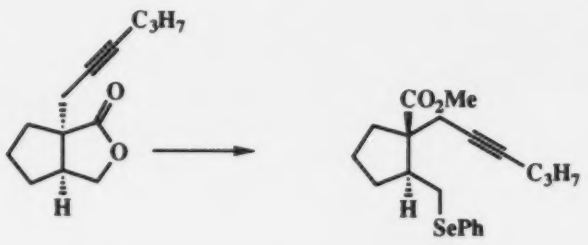


91 **97**

Lithium bis(trimethylsilyl)amide was prepared by rapid addition of *n*-butyllithium (1.45 mL, 1.57 M in hexanes, 2.27 mmol) to a stirred and cooled (-78°C) solution of bis(trimethylsilyl)amine (0.50 mL, 2.37 mmol) in THF (5 mL). The reagent was used immediately. Lactone **91**[17] (260 mg, 2.06 mmol) in THF (2 mL plus 1 mL rinse) was injected dropwise over 5 min and the resulting solution was stirred at -78°C. After 40 min propargyl bromide **123** (0.39 mL, 3.09 mmol) was

injected neat, and the cooling bath was removed. Stirring was continued overnight. The mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether (3 x 30 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate-hexane, gave **97** (268 mg, 63%) as a pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2956, 2200, 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.96 (t, J = 7.0 Hz, 3 H), 1.44-1.81 (m, 6 H), 1.94-2.05 (m, 1 H), 2.07-2.16 (m, 3 H), 2.41 (dt, J = 16.5, 2.5 Hz, 1 H), 2.66 (dt, J = 16.5, 2.5 Hz, 1 H), 2.83-2.90 (m, 1 H), 3.94 (dd, J = 9.0, 3.5 Hz, 1 H), 4.47 (dd, J = 9.0, 4.5 Hz, 1 H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 13.45, 20.64, 22.34, 25.70, 26.32, 34.60, 37.37, 43.52, 55.35, 73.11, 75.74, 82.23, 181.89; exact mass, *m/z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1290. An analytical sample was prepared by Kugelrohr distillation (140°C, 8 mm Hg): Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.63; H, 8.70.

Methyl *cis*-1-(2-Hexynyl)-2-[(phenylseleno)methyl]-cyclopentanecarboxylate (98).

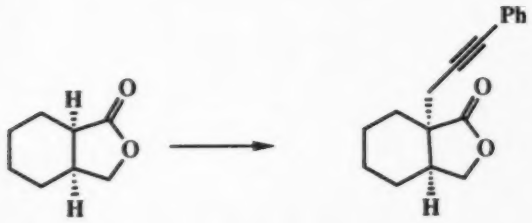


97 **98**

The literature procedure for the cleavage of lactones using phenyl selenide anion[20] was followed with slight modification: Diphenyl diselenide (293 mg, 0.94 mmol) and sodium hydride (68 mg, 60% dispersion in oil, 1.69 mmol) in THF (2.5 mL) were refluxed for 50 min. Hexamethylphosphoramide (HMPA) (0.15 mL) was added to the cooled reaction mixture followed by lactone **97** (257 mg, 1.25 mmol) in THF (0.5 mL plus 0.5 mL rinse). The mixture was refluxed for 4 h, cooled to room temperature and quenched by addition of methanol (1 mL). Solvents were evaporated and water (4 mL) was addded to the residue. The mixture was extracted with ether (20 mL) and the aqueous layer was then acidified with 6N HCl. The acidic solution was extracted with ether (3 x 50 mL) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in ether (5 mL) and diazomethane in ether was added until nitrogen evolution ceased. Evaporation of the solution and flash chromatography of the residue over silica gel (2 x 20 cm), using 5% ethyl acetate-hexane, gave selenide **98** (381 mg, 81%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.36-2.00 (m, 6 H), 2.00-2.36 (m, 5 H), 2.42 (dt, J = 16.5, 2.5 Hz, 1 H), 2.63 (dt, J = 16.5, 2.2 Hz, 1 H), 2.65 (d, J = 11.0 Hz, 1 H), 3.12 (dd, J = 11.0 Hz, 1 H), 3.71 (s, 3 H), 7.22-7.35 (m, 3 H), 7.45-7,58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.42, 20.71, 22.41, 22.63, 26.70, 29.30, 32.14, 34.72, 48.77, 51.67, 56.66, 76.73, 82.07, 126.69, 129.04, 130.66, 132.23, 175.44. An analytical sample

was prepared by Kugelrohr distillation (120°C, 0.005 mm Hg): Anal. Calcd. for $C_{20}H_{26}O_2Se$: C, 63.65; H, 6.94; O, 8.48. Found: C, 63.85; H, 6.84; O, 8.76.

cis-Hexahydro-7a-(3-phenyl-2-propynyl)-1(3_H_)-isobenzofuranone (100).

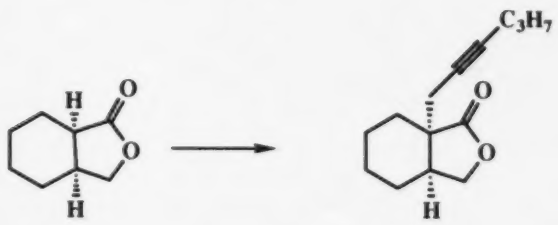


93 **100**

The procedure employed for **97** was followed using *n*-butyllithium (5.7 mL, 1.57 M in hexanes, 8.93 mmol), diisopropylamine (1.3 mL, 9.32 mmol), lactone **93** (1088 mg, 7.76 mmol) and phenyl propargyl bromide **122** (1.7 mL, 11.6 mmol). Flash chromatography of the crude product over silica gel (5 x 18 cm), using 15% ethyl acetate-hexane, gave **100** (1911 mg, 97%) as a pure [^{1}H NMR], pale yellow oil which solidified on standing: FT-IR ($CHCl_3$ cast) 2934, 1769, 1490, 1164, 1111, 1072, 1024, 757, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.35-1.97 (m, 8 H), 2.60-2.86 (m, 3 H), 4.00 (dd, J = 9.0, 5.5 Hz, 1 H), 4.34 (dd, J = 9.0, 6.5 Hz, 1 H), 7.18-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 21.88, 21.93, 25.11, 25.71, 29.32, 37.72, 45.45, 69.43, 83.80, 85.17, 123.07, 128.26, 131.67, 179.69; exact mass, *m/z* calcd for $C_{17}H_{18}O_2$ 254.1307, found 254.1304. An analytical sample was prepared by

recrystallization from dichloromethane-hexane (mp. 65°C). Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.21, H, 6.92.

cis-7a-(2-Hexynyl)hexahydro-1(3*H*)-isobenzofuranone (101).

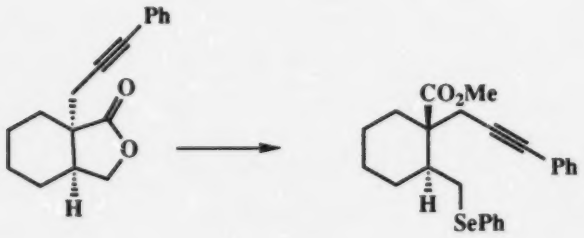


93 **101**

The procedure employed for **97** was followed using *n*-butyllithium (4.84 mL, 1.56 M in hexanes, 7.55 mmol), diisopropylamine (1.10 mL, 7.88 mmol) in THF (8 mL), lactone **93** (920 mg, 6.57 mmol) in THF (5 mL plus 1 mL rinse) and the propargyl bromide **123** (1.25 mL, 9.85 mmol). Flash chromatography of the crude product over silica gel (4 x 17 cm), using 8% ethyl acetate-hexane, gave **101** (1.270 g, 88%) as a pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2924, 1772, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.0 Hz, 3 H), 1.32-1.70 (m, 8 H), 1.72-1.87 (m, 2 H), 2.14 (tt, J = 7.0, 2.5 Hz, 2 H), 2.41 (dt, J = 8.0, 2.5 Hz, 1 H), 2.52 (dt, J = 8.0, 2.5 Hz, 1 H), 2.66-2.75 (m, 1 H), 3.98 (dd, J = 9.0, 6.0 Hz, 1 H), 4.34 (dd, J = 9.0, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 13.44, 20.70, 21.91, 22.00, 22.30, 25.12, 25.19, 29.15, 37.48, 45.45, 69.44, 75.34, 83.71, 179.92; exact mass,

m/z calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1458. An analytical sample was prepared by Kugelrohr distillation (98°C, 0.005 mm Hg). Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.17; H, 9.30.

Methyl *cis*-1-(3-phenyl-2-propynyl)-2-[(phenylseleno)-methyl]cyclohexanecarboxylate (102).

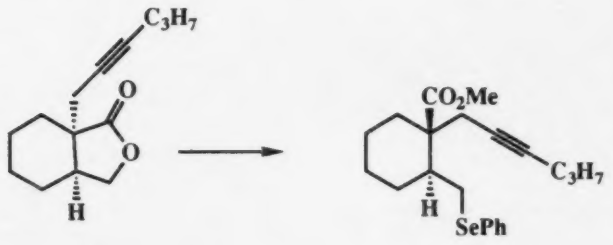


100 **102**

The procedure employed for **98** was followed using diphenyl diselenide (1.800 g, 5.77 mmol), sodium hydride (415 mg, 60% in oil, 10.38 mmol), HMPA (0.90 mL, 5.2 mmol) and lactone **100** (1.907 g, 7.50 mmol). Flash chromatography of the crude product over silica gel (5 x 16 cm), using first 8% ethyl acetate-hexane and then 15% ethyl acetate-hexane, gave unreacted lactone **100** (542 mg, 27%) and selenide **102** (2.296 g, 72%, 100% corrected for recovered starting material) as a pure [^{1}H NMR], pale yellow oil: FT-IR (CCl_4 cast) 2936, 1729, 1210, 1135, 1070, 1046, 1023, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.20-1.80 (m, 6 H), 1.91-2.10 (m, 3 H), 2.79 (dd, J = 27.0, 17.0 Hz, 2 H), 3.0 (t, J = 11.0 Hz, 1 H), 3.29 (dd, J = 11.0, 2.0 Hz, 1 H), 3.68 (s, 3 H), 7.12-7.40 (m, 8 H),

7.44-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 22.63, 24.16, 27.04, 28.15, 30.16,32.53, 43.59, 50.72, 51.63, 83.67, 85.74, 123.46, 126,67, 127.82, 128.98, 130.91, 131.63, 132.46, 174.98; exact mass, *m/z* calcd for $C_{24}H_{26}O_2Se$ 426.1097, found 426.1091. A satisfactory combustion analysis could not be obtained.

Methyl *cis*-1-(2-Hexynyl)-2-[(phenylseleno)methyl]-cyclohexanecarboxylate (103).

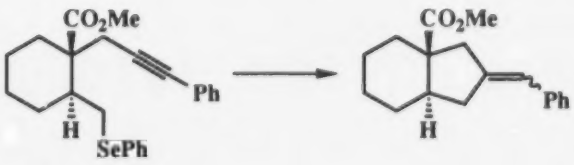


101 **103**

The procedure employed for **98** was followed using diphenyl diselenide (234 mg, 0.75 mmol), sodium hydride (54 mg, 60% in oil, 1.35 mmol) in THF (10 mL), HMPA (0.15 mL, 0.86 mmol), and lactone **101** (215 mg, 0.97 mmol) in THF (3 mL plus 1 mL rinse). Flash chromatography of the crude product over silica gel (3 x 18 cm), using first 5% ethyl acetate-hexane and then 10% ethyl acetate-hexane, gave recovered lactone **101** (24 mg, 11%) and selenide **103** (294 mg, 77%; 87% corrected for recovered starting material) as a pure [^1H NMR], pale yellow oil: FT-IR ($CHCl_3$ cast) 2933, 1730, 1209 cm^{-1}; ^1H NMR($CDCl_3$ 300 MHz) δ 0.94 (t, *J* = 7.0 Hz, 3 H), 1.20-

1.35 (m, 1 H), 1.40-1.68 (m, 7 H), 1.84-1.98 (m, 3 H), 2.07 (tt, J = 7.0, 2.5 Hz, 2 H), 2.45 (dt, J = 17.0, 2.5 Hz, 1 H) 2.58 (dt, J = 17.0, 2.5 Hz, 1 H), 2.95 (dd, J = 12.0, 11.0 Hz, 1 H), 3.20 (dd, J = 12.0, 2.5 Hz, 1 H), 7.20-7.30 (m, 3 H), 7.45-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.53, 20.79, 22.44, 22.64, 24.14, 26.99, 27.59, 30.21, 32.16, 43.47, 50.66, 51.54, 75.74, 83.51, 126.65, 128.99, 131.10, 132.47, 175.31; exact mass, m/z calcd for $C_{21}H_{28}O_2Se$ 392.1254, found 392.1251. An analytical sample was prepared by Kugelrohr distillation (127°C, 0.005 mm Hg). Anal. Calcd for $C_{21}H_{28}O_2Se$: C, 64.44; H, 7.21; O, 8.18. Found: C, 64.38; H, 7.22; O, 8.40.

Methyl (2*E*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-carboxylate and Methyl (2*Z*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-carboxylate (104).

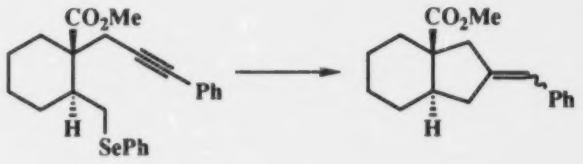


102 **104**

The general procedure for radical cyclization was followed using selenide **102** (852 mg, 2.0 mmol) in benzene (80mL), triphenyltin hydride (1054 mg, 3.0 mmol) in benzene (20 mL), and AIBN (33 mg, 0.2 mmol) in benzene (20 mL). The crude product was taken up in ether (20 mL) and a saturated

solution of iodine in ether was added until the iodine color persisted. The solution was washed with 10% sodium thiosulfate (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using first 5% dichloromethane-hexane and then mixtures od dichloromethane and hexane containing increasing amounts (up to 20%) of dichloromethane, followed by Kugelrohr distillation (97°C, 0.01 mm Hg), gave **104** (520 mg, 96%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1.3:1 ratio (^{1}H NMR): FT-IR (CCl_4 cast) 2920, 2848, 1730, 1444, 1132, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.18-1.48 (m, 3 H), 1.59-1.97 (m, 5 H), 2.37-3.12 (m, 5 H), 3.59 (s, 1.5 H), 3.65 (s, 1.5 H), 6.30-6.42 (m, 1 H), 7.14-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 23.79, 25.67, 25.92, 26.31,35.52, 36.02, 36.53, 36.36, 44.07, 48.05, 48.28, 49.61, 51.32, 52.95, 54.20, 122.69, 122.97, 125.83, 125.88, 128.02, 128.20, 138.44, 138.55, 142.55, 142.64, 175.85; exact mass, *m/z* calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1620. Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.59; H, 7.89.

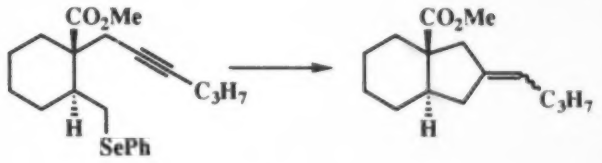
Methyl (2*E*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-carboxylate and Methyl (2*Z*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-carboxylate (104).



102 **104**

Triethylborane (1.0 mL, 1M in hexane, 1.0 mmol) was added dropwise to a stirred solution of selenide **102** (426 mg, 1.0 mmol) and triphenyltin hydride (421 mg, 1.2 mmol) in hexane (100 mL) at room temperature (protection from moisture by a drying tube packed with Drierite). Stirring was continued for 48 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 10% dichloromethane-hexane, followed Kugelrohr distillation (102°C, 0.01 mm Hg), gave **104** (236 mg, 87%) as a colorless oil, identical (^{1}H NMR) to material obtained by the general procedure for radical cyclization.

Methyl (2*E*,3aα,7aβ)-2-Butylideneoctahydro-3a*H*-indene-3a-carboxylate (105a) and Methyl (2*Z*,3aα,7aβ)-2-Butylideneoctahydro-3a*H*-indene-3a-carboxylate (105b).

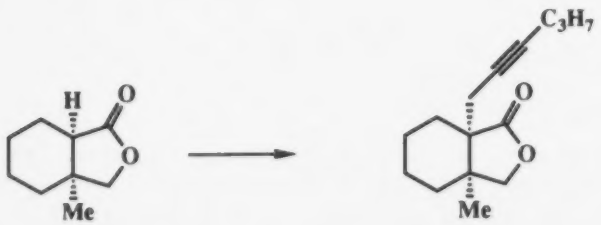


103 **105**

The general procedure for radical cyclization was followed using selenide **103** (751 mg, 1.92 mmol) in benzene (75 mL), triphenyltin hydride (110 mg, 2.88 mmol) in benzene (20 mL), and AIBN (32 mg, 0.19 mmol) in benzene (20 mL). The crude product was dissolved in ether (15 mL) and a saturated solution of iodine in ether was added until the iodine color persisted. The solution was washed with 10% sodium thiosulfate (25 mL) and brine (25 mL), and the combined aqueous washes were extracted once with ether (25 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 21 cm), using first 0.5% dichloromethane-hexane and then 10% dichloromethane-hexane, gave **105** (372 mg, 82%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1.3:1 ratio (^{1}H NMR): FT-IR ($CHCl_3$ cast) 2961, 2926, 1734, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.90 (m, 3 H), 1.13-1.40 (m, 5 H), 1.47-2.06 (m, 7.5 H), 2.15-2.75 (m, 4.5 H), 3.63 (two s, 3 H), 5.19-5.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.77, 13.83,

22.71, 22.77, 23.88, 25.91, 26.08, 26.42, 26.45, 31.56, 32.74, 36.17, 36.22, 36.48, 41.91, 46.15, 48.76, 48.82, 51.19, 53.45, 53.53, 122.46, 122.53, 138.80, 138.99, 176.17, 176.30; exact mass, *m/z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1780. An analytical sample was prepared by Kugelrohr distillation (71°C, 0.01 mm Hg). Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.23; H, 10.23. Found: C, 76.45, H, 10.24.

cis-7a-(2-Hexynyl)hexahydro-3a-methyl-1(3_H_)-isobenzofuranone (107).

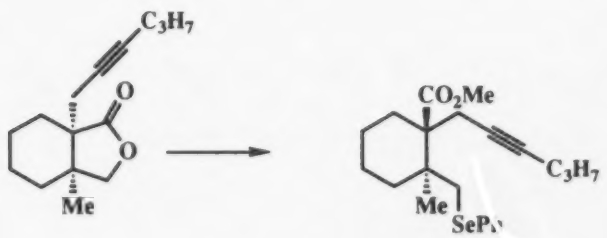


94 **107**

The procedure employed for **97** was followed using *n*-butyllithium (5.03 mL, 1.56 M in hexane, 7.85 mmol), diisopropylamine (1.15 mL, 8.19 mmol) in THF (8 mL), lactone **94** (1053 mg, 6.83 mmol) in THF (5 mL plus 1 mL rinse), and propargyl bromide **123** (1.3 mL, 10.2 mmol). Flash chromatography of the crude product over silica gel (4 x 18 cm), using 10% ethyl acetate-hexane, gave **107** (1.432 g, 90%) as a pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2933, 1773, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.0 Hz, 3 H), 1.16 (s, 3 H), 1.23-1.74 (m, 9 H), 1.96-2.06 (m, 1 H), 2.12 (tt, J = 7.0, 2.5 Hz, 2 H), 2.31 (dt, J = 17.0, 2.5 Hz,

1 H), 2.38 (dt, J = 17.0, 2,5 Hz, 1 H), 3.85 (d, J = 8.5 Hz, 1 H), 4.15 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.57, 18.26, 20.84, 21.45, 22.22, 22.95, 24.86, 29.54, 35.99, 41.05, 48.53, 75.46, 76.07, 83.53, 179.69; exact mass, *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619. An analytical sample was prepared by Kugelrohr distillation (100°C, 0.005 mm Hg). Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.08; H, 9.46.

Methyl *cis*-1-(2-Hexynyl)-2-methyl-2-[(phenylseleno)-methyl]cyclohexanecarboxylate (109).

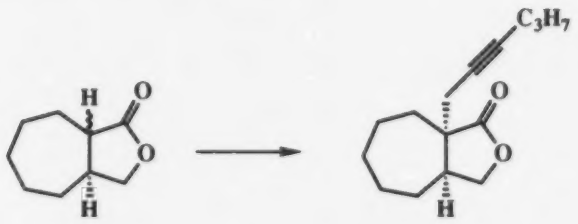


107 **109**

The procedure employed for **98** was followed using diphenyl diselenide (175 mg, 0.56 mmol), sodium hydride (40 mg, 60% dispersion in oil, 1.0 mmol), THF (2 mL), 18-crown-6 (10 mg, 0.04 mmol), and lactone **107** (171 mg, 0.73 mmol) in THF (1 mL plus 0.5 mL rinse). The mixture was refluxed for 90 h. Flash chromatography of the crude product over silica gel (2 x 18 cm), using first 3% ethyl acetate-hexane and then 10% ethyl acetate-hexane, gave unreacted lactone **107** (140 mg, 82%) and selenide **109** (42 mg, 14%; 79% corrected for recovered starting material) as a pure [^1H NMR], pale yellow

oil: FT-IR ($CHCl_3$ cast) 2931, 1726, 1201, 734 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.92 (t, *J* = 7.5 Hz, 3 H), 1.09 (s, 3 H), 1.14-1.52 (m, 6 H), 1.55-1.65 (m, 1 H), 1.70-1.80 (m, 1 H), 1.97-2.13 [m, including tt (*J* = 7.0, 2.5 Hz) at δ 2.07, 4 H], 2.49 (dt, *J* = 15.0, 2.5 Hz, 1 H), 2.73 (br d, *J* = 12.0 Hz, 1 H), 2.88 (br d, *J* = 16.0 Hz, 1 H), 3.45 (br d, *J* = 12.0 Hz, 1 H), 3.70 (s, 3 H), 7.20-7.30 (m, 3 H), 7.44-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.34, 20.74, 21.04, 21.31, 22.13, 22.43, 23.00, 27.03, 33.65, 38.11, 39.54, 51.64, 53.06, 76.66, 82.64, 126.85, 129.03, 131.32, 133.01, 175.15; exact mass, *m/z* calcd for $C_{22}H_{30}O_2Se$ 406.1410, found 406.1419. An analytical sample was prepared by Kugelrohr distillation (137°C, 0.008 mm Hg). Anal. Calcd. for $C_{22}H_{30}O_2Se$: C, 65.17; H, 7.46; O, 7.89. Found: C, 65.24; H, 7.43; O, 7.73.

cis-8a-(2-Hexynyl)octahydro-1_H_-cyclohepta[c]-furan-1-one (116a) and _trans_-8a-(2-Hexynyl)octahydro-1_H_-cyclohepta[c]-furan-1-one (116b).



95 **116**

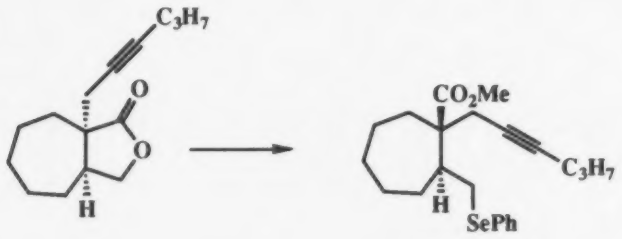
Lithium bis(trimethylsilyl)amide was prepared by rapid addition of *n*-butyllithium (8.84 mL, 1.6 M solution in hexane, 14.1 mmol to a stirred and cooled (-78°C) solution of

bis(trimethylsilyl)amine (3.11 mL, 14.7 mmol) in THF (20 mL). The reagent was used immediately. Lactone **95** (1817 mg, 11.8 mmol) in THF (10 mL plus 3 mL rinse) was injected dropwise over 5 min and the resulting solution was stirred for 40 min at -78°C. The propargyl bromide **123** (2.23 mL, 17.7 mmol) was injected neat, and the cooling bath was removed. Stirring was continued overnight. The mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether (3 x 30 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 5% ethyl acetate-hexane, gave the *cis* isomer **116a** (2451 mg, 89%) as a pure [^{1}H NMR] colorless liquid: FT-IR ($CHCl_3$ cast) 2920, 1766, 430 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.0 Hz, 3 H), 1.43-1.78 (m, 10 H), 1.79-1.87 (m, 2 H), 2.13 (tt, J = 7.0, 2.4 Hz, 2 H), 2.43 (dt, J = 17.0, 3.0 Hz, 1 H), 2.50 (dt, J = 17.0, 3.0 Hz, 1 H), 2.68-2.78 (m, 1 H), 3.95 (dd, J = 9.0, 4.5 Hz, 1 H), 4.47 (dd, J = 9.0, 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.52, 20.76, 22.33, 24.75, 26.63, 29.99, 30.92, 31.76, 34.73, 43.15, 50.86, 71.58, 75.52, 82.96, 181.53; exact mass, *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found: 234.1616. An analytical sample was prepared by Kugelrohr distillation (72°C, 0.075 mm Hg). Anal Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.04; H, 9.35.

The *trans* isomer **116b** (17 mg, 0.6%) was also isolated as a colorless oil, which contained trace impurities [^{1}H NMR]: FT-IR (CCl_4 cast) 2961, 2932, 2064, 1772, 1174, 1164, 1114,

1025 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.96 (t, J = 7.5 Hz, 3 H), 1.30-2.00 (m, 12 H), 2.12 (tt, J = 7.0, 2.5 Hz, 2 H), 2.41 (dt, J = 16.0, 2.5 Hz, 1 H), 2.60 (dt, J = 16.0, 2.5 Hz, 1 H), 2.63-2.77 (m, 1 H), 4.09-4.24 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.52, 20.80, 21.27, 22.14, 22.26, 25.58, 26.02, 26.23, 36.68, 43.38, 49.01, 70.48, 75.12, 83.38, 180.76; exact mass, *m/z* calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1616.

Methyl *cis*-1-(2-Hexynyl)-2-[(phenylseleno)methyl]-cycloheptanecarboxylate (117).

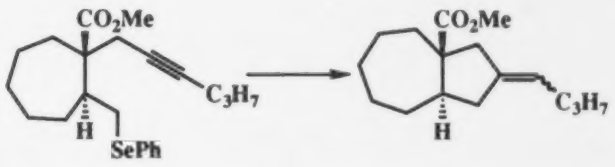


116 **117**

The procedure employed for **98** was followed using diphenyl diselenide (387 mg, 1.24 mmol), sodium hydride (89 mg, 60% dispersion in oil, 2.23 mmol), HMPA (0.20 mL, 1.15 mmol) and lactone **116a** (368 mg, 1.57 mmol). Flash chromatography of the crude product over silica gel (3 x 20 cm), using 3% ethyl acetate-hexane followed by 10% ethyl acetate-hexane, gave unreacted lactone **116** (89 mg, 24%) and selenide **117** (417 mg, 66%, 86% corrected for recovered starting material) as a pure [^1H NMR], pale yellow oil: FT-IR ($CHCl_3$ cast) 2928, 1727, 1437, 1195, 1175, 737 cm^{-1}; ^1H NMR

($CDCl_3$ 200 MHz) δ 0.95 (t, *J* = 7.0 Hz, 3 H), 1.30-1.97 (m, 11 H), 1.97-2.20 (m, 4 H), 2.28 (dt, *J* = 16.0, 2.5 Hz, 1 H), 2.47-2.70 (m, 2 H), 3.15 (dd, *J* = 12.0, 2.0 Hz, 1 H), 3.68 (s, 3 H), 7.21-7.34 (m, 3 H), 7.46-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.44, 20.76, 22.36, 22.62, 27.27, 28.31, 28.35, 29.41, 32.18, 34.67, 46.41, 51.57, 53.39, 76.83, 82.57, 126.96, 129.00, 130.38, 133.09, 175.55; exact mass, *m/z* calcd for $C_{22}H_{30}O_2Se$ 406.1410, found 406.1423. An analytical sample was prepared by Kugelrohr distillation (104°C, 0.005 mm Hg). Anal. Calcd. for $C_{22}H_{30}O_2Se$: C, 65.17; H, 7.46; O, 7.89. Found: C, 65.21; H, 7.21; O, 8.14.

Methyl (2*E*,3aα,8aβ)-2-Butylideneoctahydro-3a(1*H*)-azulenecarboxylate (118a) and Methyl (2*Z*,3aα,8aβ)-2-Butylideneoctahydro-3a(1*H*)-azulenecarboxylate (118b).

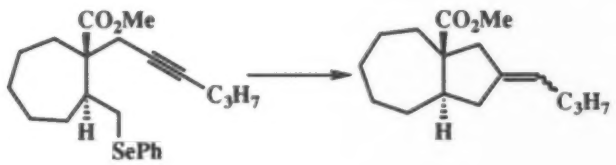


117 **118**

The general procedure for radical cyclization was followed using selenide **117** (417 mg, 1.03 mmol) in benzene (30 mL), triphenyltin hydride (542 mg, 1.55 mmol) in benzene (10 mL), and AIBN (17 mg, 0.10 mmol) in benzene (10 mL). At the end of the reaction the solvent was evaporated and Kugelrohr distillation (125-135°C, 0.05 mm Hg) of the residue, followed by flash chromatography over silica gel (2

x 18 cm), using 2% ethyl acetate-hexane, gave **118** (202 mg, 79%) as a pure [^{1}H NMR] colorless oil, which was a chromatographically (TLC) inseparable mixture of two isomers in about a 1:1.2 ratio (^{13}C NMR): FT-IR ($CHCl_3$ cast) 2926, 2856, 1729, 1452, 1195, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.82-0.91 (m, 3 H), 1.15-2.10 (m, 14 H), 2.15-2.74 (m, 5 H), 3.67 (two s, 3 H), 5.07-5.20 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.80, 13.82, 22.75, 22.79, 26.21, 27.25, 27.31, 27.96, 28.12, 29.55, 30.09, 31.45, 31.51, 37.31, 39.18, 39.79, 41.07, 45.46, 47.99, 48.20, 49.68, 51.14, 51.18, 54.96, 55.01, 120.66, 120.80, 139.77, 139.93, 176.93, 177.17; exact mass, *m/z* calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1934. Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.96; H, 10.49.

Methyl (2*E*,3aα,8aβ)-2-Butylideneoctahydro-3a(1*H*)-azulenecarboxylate (118a) and Methyl (2*Z*,3aα,8aβ)-2-Butylideneoctahydro-3a(1*H*)-azulenecarboxylate (118b).

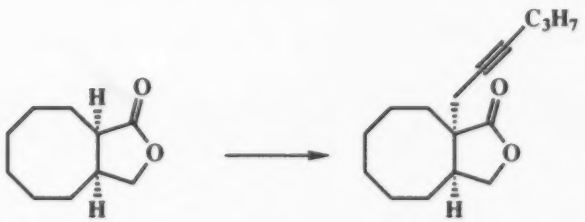


117 **118**

Triethylborane (1.0 mL, 1M in hexane, 1.0 mmol) was added dropwise to a stirred solution of selenide **117** (406 mg, 1.0 mmol) and triphenyltin hydride (422 mg, 1.2 mmol) in hexane (100 mL) at room temperature (protection from moisture

by a drying tube packed with Drierite). The mixture was stirred for 24 h, and then evaporated. The residue was taken up in ether (10 mL) and a saturated solution of iodine in ether was added dropwise until the iodine color persisted. The resulting solution was washed with 10% sodium thiosulfate (15 mL), and brine (15 mL), and the combined aqueous washes were extracted with ether (15 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 17 cm), using 5% dichloromethane-hexane followed by 10% dichloromethane-hexane, gave **118** (237 mg, 95%) as a pure [^{1}H NMR] colorless oil, identical (^{1}H NMR) to material obtained by the general procedure for radical cyclization.

cis-9a-(2-Hexynyl)octahydrocycloocta[c]furan-1(3_H_)-one (119).

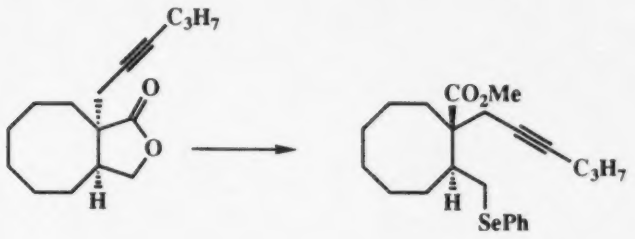


96 **119**

Lithium diisopropylamide was prepared by rapid addition of *n*-butyllithium (3.5 mL, 1.56 M solution in hexanes, 5.5 mmol) to a stirred and cooled (-78°C) solution of diisopropylamine (0.84 mL, 6.0 mmol) in THF (6 mL). The reagent was used immediately. Lactone **96** (841 mg, 5.0 mmol)

in THF (4 mL plus 1 mL rinse) was added dropwise over 5 min. and the resulting solution was stirred for 40 min at -78°C. Propargyl bromide **123** (1.0 mL, 7.6 mmol) was added neat. Stirring was continued at -78 °C for 2 h and then at ca 0°C (ice-bath) for 1 h. The reaction was quenched with saturated aqueous amonium chloride (10 mL) and the mixture was extracted with ether (3 x 30 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 5% ethyl acetate-hexane, gave **119** (900 mg, 72%) as a pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2928, 2860, 1772, 1464, 1190, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.5 Hz, 3 H), 1.20-1.93 [m, including q at δ 1.51 (J = 14.5), 13 H], 1.98-2.09 (m, 1 H), 2.13 (tt, J = 7.0, 2.5 Hz, 2 H), 2.35-2.44 (m, 1 H), 2.45 (dt, J = 17.0, 2.2 Hz, 1 H), 2.53 (dt, J = 17.0, 2.2 Hz, 1 H), 3.88 (dd, J = 9.0, 2.2 Hz, 1 H), 4.57 (dd, J = 9.0, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.46, 20.74, 22.21, 23.64, 25.10, 25.61, 25.92, 27.64, 30.142, 32.10, 44.69, 48.95, 74.62, 75.09, 83.37, 180.60; exact mass, *m/z* calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1774. An analytical sample was prepared by Kugelrohr distillation (110°C, 0.01mm Hg). Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.37; H, 9.66.

Methyl *cis*-1-(2-Hexynyl)-2-[(phenylseleno)methyl]-cyclooctanecarboxylate (120).

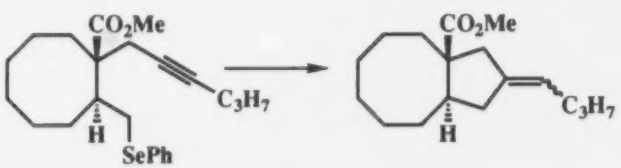


119 **120**

The literature procedure for cleavage of lactones using phenyl selenide anion[20] was followed with minor modifications: Diphenyl diselenide (767 mg, 2.46 mmol) and sodium hydride (177 mg, 60% dispersion in oil, 4.43 mmol) in THF (8 mL) were refluxed for 50 min. Hexamethylphosphoramide (HMPA) (0.50 mL, 2.9 mmol) was added to the cooled mixture, followed by lactone **119** (796 mg, 3.20 mmol) in THF (2 mL plus 1 mL rinse). The mixture was refluxed for 13 h (TLC control), cooled to room temperature and quenched by addition of methanol (4 mL). The solvents were evaporated and water was added to the residue. The mixture was extracted with ether (20 mL) and the aqueous layer was acidified with 6N HCl and extracted with ether (3 x 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in ether (5 mL) and diazomethane in ether was added until nitrogen evolution ceased. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 18 cm), using 3% ethyl acetate-hexane followed by 10% ethyl acetate-hexane, gave unreacted lactone **119** (159 mg, 19%) and

selenide **120** (983 mg, 69%, 85% corrected for recovered starting material) as a pure [^{1}H NMR], pale yellow oil: FT-IR ($CHCl_3$ cast) 2926, 1728, 1204, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.93 (t, J = 7.5 Hz, 3 H), 1.20-1.72 [m, including q at δ 1.46 (J = 7.5 Hz), 10 H], 1.72-1.87 (m, 2 H), 1.87-2.13 (m, 5 H), 2.16-2.28 (m, 1 H), 2.35 (t, J = 11.5 Hz, 1 H), 2.72 (br d, J = 12.0 Hz, 1 H), 3.23 (dd, J = 12.0, 2.0 Hz, 1 H), 3.68 (s, 3 H), 7.22-7.31 (m, 3 H), 7.46-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.44, 20.80, 22.41, 23.36, 25.38, 25.84, 27.03, 30.19, 30.27, 30.44, 33.98, 43.23, 51.53, 52.98, 76.91, 82.53, 127.08, 129.07, 130.22, 133.28, 175.06; exact mass, *m/z* calcd for $C_{23}H_{32}O_2Se$ 420.1567, found 420.1575. An analytical sample was prepared by Kugelrohr distillation (145°C, 0.01 mm Hg). Anal. Calcd. for $C_{23}H_{32}O_2Se$: C, 65.86; H, 7.69; O, 7.63. Found: C, 66.01; H, 7.67; O, 7.80.

Methyl (2*E*,3aα,9aβ)-2-Butylidenedecahydro-3a*H*-cyclopentacyclooctene-3a-carboxylate (121a) and Methyl (2*Z*,3aα,9aβ)-2-Butylidenedecahydro-3a*H*-cyclopentacyclooctene-3a-carboxylate (121b).

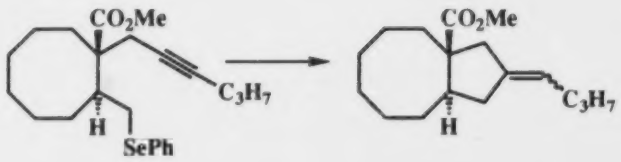


120 **121**

The general procedure for radical cyclization was followed using selenide **120** (426 mg, 1.0 mmol) in benzene (40

mL), triphenyltin hydride (534 mg, 1.5 mmol) in benzene (10 mL), and AIBN (17 mg, 0.1 mmol) in benzene (10 mL). The crude product was taken up in ether (25 mL) and a saturated solution of iodine in ether was added dropwise until the iodine color persisted. The solution was washed with 10% sodium thiosulfate (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using first 5% dichloromethane-hexane followed by 10% dichloromethane-hexane, gave **121** (206 mg, 77%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1:1 ratio (^{1}H NMR): FT-IR ($CHCl_3$ cast) 2952, 2925, 2870, 1727, 1202, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.88 (t, J = 7.5 Hz, 1.5 H), 0.89 (t, J = 7.5 Hz, 1.5 H), 1.24-1.77 (m, 13 H), 1.86-1.97 (m, 2 H), 2.06-2.51 (m, 5 H), [2.59 (d, J = 16.0 Hz) and 2.71 (d, J = 17.0 Hz), 1 H], 3.65 (s, 1.5 H), 3.66 (s, 1.5 H), 5.12-5.23 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.83, 13.85, 22.75, 22.78, 22.80, 24.94, 25.10, 26.60, 30.70, 30.77, 30.81, 30.96, 31.39, 35.69, 36.02, 37.12, 40.82, 42.52, 42.73, 42.78, 46.99, 51.23, 51.29, 54.45, 54.71, 120.41, 120.54, 139.18, 177.16, 177.26; exact mass, *m/z* calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2089. An analytical sample was prepared by Kugelrohr distillation (85°C, 0.01 mm Hg). Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.38; H, 10.97.

Methyl (2*E*, 3aα, 9aβ)-2-Butylidenedecahydro-3a*H*-cyclopentacyclooctene-3a-carboxylate (121a) and Methyl (2*Z*, 3aα, 9aβ)-2-Butylidenedecahydro-3a*H*-cyclopentacyclooctene-3a-carboxylate (121b).



120 **121**

Triethylborane (1.3 mL, 1 M in hexane, 1.3 mmol) was added dropwise to a stirred solution of selenide **120** (559 mg, 1.33 mmol) and triphenyltin hydride (561 mg, 1.6 mmol) in hexane (130 mL) at room temperature (protection from moisture by a drying tube packed with Drierite). After 24 h the solvent was evaporated and the residue was taken up in ether (25 mL). A saturated solution of iodine in ether was added dropwise until the iodine color persisted. The solution was washed with 10% sodium thiosulfate (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 14 cm), using 3% ethyl acetate-hexane, gave **121** (306 mg, 87%) as a colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers identical (^1H NMR) to material obtained by the general procedure for radical cyclization.

Se-Phenyl *O*-[2-cyclohexene-1-yl)methyl]carbonoselenoate (124).

124

Phosgene (ca 6 mL) was condensed in a cooled (-78°C) three-necked 200-mL flask. A solution of 2-cyclohexenylmethanol[32] (2.241 g, 20 mmol) and triethylamine (3.3 mL, 24 mmol) in THF (20 mL) was added dropwise (ca 10 min). The cold bath was removed and stirring was continued for 40 min. The mixture was then concentrated under reduced pressure to about half its original volume, and a solution of benzeneselenol (2.76 mL, 26 mmol) and pyridine (1.9 mL, 24.6 mmol) in THF (20 mL) was added with stirring (argon atmosphere). After 45 min the mixture was quenched with water (30 mL) and extracted with ether (3 x 25 mL). The combined ether extracts were washed with brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 16 cm), using 5% dichloromethane-hexane, gave **124** (4.952 g, 84%) as a pure [^{1}H NMR], pale yellow oil: FT-IR (neat film) 2931, 1729, 1478, 1439, 1121, 1074, 1022, 739, 723, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.25-1.40 (m, 1 H), 1.46-1.62 (m, 1 H), 1.65-1.82 (m, 2 H), 1.94-2.40 (m, 2 H), 2.40-2.54 (m, 1 H), 4.18 (d, J = 13.5 Hz, 2 H), 5.47-5.55 (m, 1 H), 5.75-5.84 (m, 1 H), 7.30-7.45 (m, 3 H), 7.58-7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 20.50, 25.13, 25.49,

34.95, 71.60, 126.13, 126.34, 129.10, 129.27, 129.94, 135.83, 166.96; exact mass, *m/z* calcd for $C_{14}H_{16}O_2Se$ 296.0315, found 296.0321. An analytical sample was prepared by Kugelrohr distillation (135°C, 12 mm Hg). Anal. Calcd. for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46; O, 10.84. Found: C, 57.20; H, 5.58; O, 10.74.

(3aα,7α,7aα)-Hexahydro-7-(2-propenyl)-1(3*H*)-isobenzofuranone (126).

124 **126**

A solution of selenide **124** (1471 mg, 5.0 mmol), allyltributyltin (7.7 mL, 25 mmol) and hexabutylditin (0.26 mL, 0.51 mmol), in benzene (10 mL), was irradiated for 24 h with a sun lamp (General Electric, 275 W) placed about 5 cm from the reaction flask. Evaporation of the solvents and flash chromatography of the residue over silica gel (5 x 14 cm), using 10% ethyl acetate-hexane, gave **126** (647 mg, 72%) as a colorless oil containing slight impurities [^{1}H NMR]: FT-IR ($CHCl_3$ cast) 2928, 1769, 1172, 1136, 988 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.24-1.59 (m, 5 H), 1.70-1.83 (m, 1 H), 2.05-2.23 (m, 2 H), 2.23-2.38 (m, 1 H), 2.43 (dd, *J* = 7.0, 3.5 Hz, 1 H), 2.47-2.60 (m, 1 H),3.99 (dd, *J* = 9.0, 3.5 Hz, 1

H), 4.19 (dd, J = 9.0, 5.5 Hz, 1 H), 5.00-5.13 (m, 2 H), 5.69-5.83 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 18.84, 26.18, 27.08, 31.80, 33.50, 37.46, 43.40, 71.39, 116.96, 136.48, 178.29; exact mass, m/z calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1149. An analytical sample was prepared by Kugelrohr distillation (140°C, 13 mm Hg). Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.41; H, 8.65%.

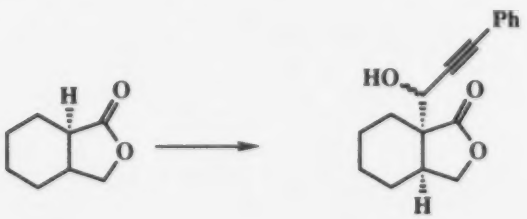
(3aα,7α,7aα)-7a-Hexylhexahydro-7-(2-propenyl)-1(3*H*)-isobenzofuranone (127).

126 **127**

The procedure employed for **97** was followed using *n*-butyllithium (2.32 mL, 1.60 M in hexanes, 3.71 mmol), diisopropylamine (0.54 mL, 3.87 mmol) in THF (3 mL), lactone **126** (581 mg, 3.23 mmol) in THF (3 mL plus 1 mL rinse), and 1-bromohexane (0.72 mL, 5.13 mmol). HMPA (0.60 mL, 3.45 mmol) was added and the resulting solution was allowed to warm to room temperature. After 4 h the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether (2 x 15 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 14 cm), using 10% ethyl acetate-

hexane, gave **127** (681 mg, 80%) as a colorless oil containing trace impurities [^{1}H NMR]: FT-IR (CCl_4 cast) 2929, 2858, 1768, 1211, 1087, 1020, 1001, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.00-1.90 (m, 18 H), 2.42-2.75 (m, 2 H), 4.14 (d, *J* = 2.0 Hz, 1 H), 4.19 (s, 1 H), 4.95-5.09 (m, 2 H), 5.55-5.78 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.07, 20.79, 21.55, 22.62, 24.84, 25.07, 26.20, 29.86, 31.76, 33.80, 36.66, 37.36, 47.53, 67.19, 116.59, 137.22, 180.14; exact mass, *m/z* calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2106. An analytical sample was prepared by Kugelrohr distillation (145-148°C, 11 mm Hg). Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.23; H, 10.56.

[3aα,7aα (R*)]-Hexahydro-7a-(1-hydroxy-3-phenyl-2-propynyl)-1(3*H*)-isobenzofuranone (128a) and [3aα,7aα(S*)]-Hexahydro-7a-(1-hydroxy-3-phenyl-2-propynyl)-1(3*H*)-isobenzofuranone (128b).



93 **128**

The procedure employed for **97** was followed using *n*-butyllithium (1.40 mL, 1.6 M in hexanes, 2.24 mmol), diisopropylamine (0.35 mL, 2.5 mmol) in THF (10 mL), lactone **93** (280 mg, 2.00 mmol) in THF (3 mL and 1 mL as a rinse), and

phenyl propargyl aldehyde (380 mg, 2.92 mmol) in THF (3 mL plus 1 mL as a rinse). The reaction mixture was stirred at -78°C for 1.5 h and quenched with saturated ammonium chloride (10 mL). Flash chromatography of the crude products over silica gel (3 x 16 cm), using 25% ethyl acetate-hexane, followed by Kugelrohr distillation (125-130°C, 0.05 mm Hg), gave **128** (513 mg, 95%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1:1 ratio (^{1}H NMR): FT-IR (CCl_4 cast) 3440, 2933, 1763, 1753, 1490, 1211, 1070, 1052, 1021, 758, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.35-2.05 (m, 7 H), 2.05-2.25 (m, 1 H), 2.70-2.85 (m, 0.5 H), 2.95-3.15 (m, 1 H), 3.45-3.55 (m, 0.5 H), 4.0-4.17 (m, 1 H), 4.35-4.50 (m, 1 H), 4.72-4.87 (m, 1 H), 7.22-7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 20.54, 20.71, 21.38, 23.54, 24.88, 25.33, 25.52, 35.88, 36.68, 49.67, 65.05, 66.22, 69.71, 69.90, 86.50, 87.08, 87.20, 87.30, 122.04, 128.33, 128.79, 131.76, 179.48, 180.44; exact mass, *m/z* calcd for $C_{17}H_{18}O_3$ 270.1256, found 270.1255. Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.24; H, 6.77.

[3aα,7aα(R*)]-7a-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-phenyl-2-propynyl]hexahydro-1(3*H*)-isobenzofuranone (129a) and [3aα,7aα(S*)]-7a-[1[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-phenyl-2-propynyl]hexahydro-1(3*H*)-isobenzofuranone (129b).

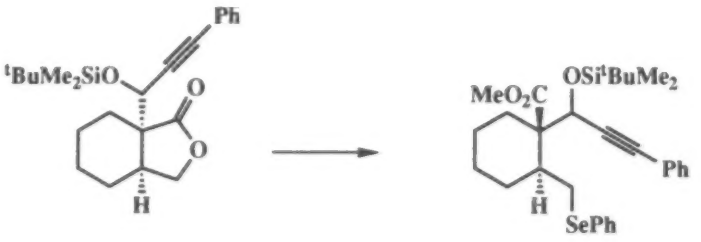
128 **129**

Triethylamine (1.3 mL, 9.5 mmol) and 4-*N*,*N*-dimethylaminopyridine (25 mg, 0.20 mmol) were added to a stirred solution of alcohols **128** (511 mg, 1.9 mmol) in DMF (2 mL). *t*-Butyldimethylsilylchloride (1430 mg, 9.5 mmol) in DMF (1.5 mL plus 0.5 mL rinse) was added and the resulting suspension was stirred for 66 h. More 4-*N*,*N*-dimethylaminopyridine (25 mg, 0.20 mmol) was added and the mixture was heated at 50°C (oil bath temperature) for 24 h, cooled, quenched with water (5 mL), and extracted with ether (3 x 20 mL). The combined ether extracts were washed with saturated ammonium chloride (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 19 cm), using 5% ethyl acetate-hexane, gave **129** (621 mg, 85%) as a pure [^{1}H NMR] colorless oil which was a mixture of two diastereomers in a 1.2:1 ratio (^{1}H NMR). The diastereomers were separated by flash chromatography. The faster moving

diastereomer (**129a**) had: FT-IR ($CHCl_3$ cast) 2930, 2857, 1770, 1088, 1082, 840, 783, 758, 690 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.15 (s, 3 H), 0.20 (s, 3 H), 0.90 (s, 9 H), 1.22-1.41 (m, 3 H), 1.52-1.63 (m, 1 H), 1.66-1.83 (m, 2 H) 1.89-2.06 (m, 2 H), 2.93-3.02 (m, 1 H), 3.88 (dd, J = 8.0, 3.5 Hz, 1 H), 4.53 (dd, J = 8.0, 6.5 Hz, 1 H),4.63 (s, 1 H), 7.30-7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ -5.49, -4.56, 18.06, 21.53, 21.65, 25.67, 27.36, 26.03, 35.51, 52.17, 69.38, 72.05, 86.71, 88.20, 122.44, 128.43, 128.66, 131.47, 179.27; exact mass, *m/z* (M -*t*-Bu) calcd for $C_{19}H_{23}O_3Si$ 327.1416, found 327.1415 ($C_{19}H_{23}O_3Si$). An analytical sample was prepared by Kugelrohr distillation (143°C, 0.008 mm Hg). Anal. Calcd. for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.52; H, 8.44.

The slower moving diastereomer (**129b**) had: FT-IR ($CHCl_3$ cast) 2929, 1772, 1070, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 3 H), 0.22 (s, 3 H), 0.94 (s, 9 H), 1.30-1.47 (m, 3 H), 1.47-1.60 (m, 1 H), 1.66-1.80 (m, 1 H), 1.80-2.04 (m, 3 H), 2.86-2.97 (m, 1 H), 3.95 (dd, J = 9.0, 5.0 Hz, 1 H), 4.50 (dd, J = 9.0, 7.0 Hz, 1 H), 4.76 (s, 1 H), 7.29-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ -5.02, -4.38, 18.25, 21.10, 21.69, 215.84, 26.52, 27.40, 36.11, 51.70, 68.15, 70.57, 86.72, 87.73, 122.43, 128.37, 128.62, 131.61, 178.35; exact mass, *m/z* (M - *t*-Bu) calcd for $C_{19}H_{23}O_3Si$ 327.1416, found 327.1418. An analytical sample was prepared by Kugelrohr distillation (140°C, 0.010 mm Hg). Anal. Calcd. for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.91; H, 8.33.

Methyl [1α,1(R*),2α]-1-[1-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]-3-phenyl-2-propynyl]-2-[(phenyl-seleno)methyl]cyclohexane carboxylate (130).



129b **130**

The procedure employed for **98** was followed using diphenyl diselenide (237 mg, 0.76 mmol), sodium hydride (55 mg, 60% dispersion in oil, 1.37 mmol), THF (2.5 mL), HMPA (0.18 mL, 1.0 mmol), and lactone **129b** (379 mg, 1.0 mmol) in THF (2 mL plus 1 mL as a rinse). After workup, flash chromatography of the residue over silica gel (a) (4 x 18 cm) using ethyl acetate-hexane mixtures (from 0% ethyl acetate to 15%); (b) (4 x 18 cm) using ethyl acetate-hexane mixtures (from 3% ethyl acetate to 5%); (c) (3 x 18 cm) using first 10% dichloromethane-hexane (to remove diphenyl diselenide) and then 5% ethyl acetate-hexane, gave selenide **130** (356 mg, 65%) as a pure [^{1}H NMR] pale yellow oil: FT-IR ($CHCl_3$ cast) 2928, 2855, 1738, 1215, 1136, 1081, 838, 778, 756, 735, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.12 (s, 3 H), 0.18 (s, 3 H), 0.88 (s, 9 H) 1.05-1.36 (m, 2 H), 1.53-1.79 (m, 4 H), 2.03-2.16 (m, 2 H), 2.23-2.32 (m, 1 H) 2.98 (dd, J = 12.0, 11.5

Hz, 1 H), 3.54 (dd, J = 12.5, 2.5 Hz, 1 H), 3.70 (s, 3 H), 5.12 (s, 1 H), 7.07-7.14 (m, 3 H), 7.29-7.37 (m, 4 H), 7.46-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ -5.31, -4.23, 18.10, 23.07, 25.69, 25.95, 28.84, 29.45, 31.08, 43.11, 51.42, 57.41, 68.00, 87.55, 87.69, 122.68, 126.49, 128.31, 128.45, 128.95, 131.32, 131.60, 132.34, 173.93; exact mass, m/z calcd for $C_{30}H_{40}O_3SiSe$ 556.1911, found 556.1920. An analytical sample was prepared by Kugelrohr distillation (158°C, 0.005 mm Hg). Anal. Calcd. for $C_{30}H_{40}O_3SiSe$: C, 64.84; H, 7.26. Found: C, 65.10; H, 7.00.

Methyl [1(R*),2*E*,3aβ,9aα]-3-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]octahydro-2-(phenyl-methylene)-3a*H*-indene-3a-carboxylate and Methyl [1(R*),2*Z*,3aβ,9aα]-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-2-(phenylmethelene)-3a*H*-indene-3a-carboxylate (131).

130 **131**

The general procedure for radical cyclization was followed using selenide **130** (327 mg, 0.59 mmol) in benzene (25 mL), triphenyltin hydride (310 mg, 0.88 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). The crude product was taken up in ether (15 mL) and a saturated

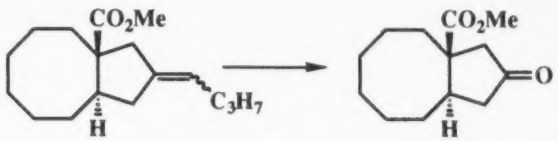
solution of iodine in ether was added until the iodine color persisted. The solution was washed with 10% aqueous sodium thiosulfate (10 mL), and with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 19 cm), using 15% dichloromethane-hexane, gave **131** (185 mg, 78%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1.6:1 ratio (^{1}H NMR): FT-IR ($CHCl_3$ cast) 2950, 2928, 2855, 1735, 1250, 1205, 1172, 1129, 1105, 1087, 1069, 854, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ -0.43 (s, 1.8 H), -0.30 (s, 1.8 H), 0.10 (s, 1.2 H) 0.17 (s, 1.2 H), 0.77 (s, 5.4 H), 0.89 (s, 3.6 H), 1.08-1.36 (m, 2 H), 1.57-1.82 (m, 4 H), 1.88-2.10 (m, 2 H), 2.13-2.30 (m, 1 H), 2.38-2.69 (m, 2 H), 3.60 (s, 1.2 H), 3.71 (s, 1.8 H), 4.49 (s, 0.4 H), 5.10 (s, 0.6 H), 6.40 (s, 0.6 H), 6.45 (t, J = 2.5 Hz, 0.4 H), 7.10-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) -5.10, -5.03, -4.25, -3.75, 18.30, 23.32, 25.54, 25.73, 25.90, 25.98, 26.29, 26.45, 30.30, 30.50, 33.55, 34.54, 40.80, 43.22, 51.43, 59.41, 60.61, 74.31, 82.77, 126.56, 126.72, 127.07, 128.31, 128.52, 137.80, 138.25, 145.13, 145.29, 174.96, 175.10; exact mass, *m/z* calcd for $C_{24}H_{36}O_3Si$ 400.2434, found 400.2428. An analytical sample was prepared by Kugelrohr distillation (123°C, 0.010 mm Hg). Anal. Calcd. for $C_{24}H_{36}O_3Si$: C, 71.95; H, 9.06. Found: C, 71.72; H, 9.23.

Methyl (3aα,7aβ)-Octahydro-2-oxo-3a*H*-indene-3a-carboxylate (132).

104 **132**

This experiment was done using the apparatus described by Rubin,[33] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a dry-ice acetone bath, was bubbled for 4 min into dry dichloromethane (19.5 mL) at -78°C. The resulting solution was transfered into the other bulb of the apparatus which contained a cold (-78°C) solution of **104** (58 mg, 0.25 mmol) in dichloromethane (4 mL) and methanol (6 mL). The resulting mixture was stirred for 5 min and triphenylphoshine (200 mg, 0.75 mmol) was added. The cold-bath was removed and stirring was continued for 1.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 17 cm), using 15% ethyl acetate-hexane followed by 20% ethyl acetate-hexane, gave **132** (35 mg, 73%) as a pure [^{1}H NMR] oil: FT-IR (CCl_4 cast) 2924, 2860, 1750, 1729, 1220, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.23-2.32 (m, 10 H), 2.40-2.70 (m, 3 H), 3.69 (s, 3 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 23.43, 25.76, 26.23, 35.70, 41.97, 47.13, 51.46, 51.72, 175.25, 215.77; exact mass, *m/z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1100. A satisfactory combustion analysis could not be obtained.

Methyl (3aα,9aβ)-Decahydro-2-oxo-3a*H*-cyclopentacyclooctene-3a-carboxylate (133).

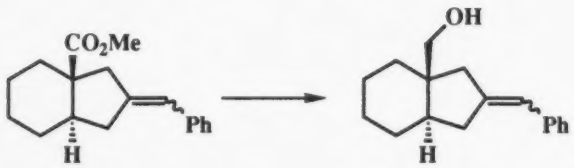


121 **133**

This experiment was done using the apparatus described by Rubin,[33] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a dry-ice acetone bath, was bubbled for 4 min into dry dichloromethane (21 mL) at -78°C. The resulting solution was transfered into the other bulb of the apparatus which contained a cold (-78°C) solution of **121** (67 mg, 0.25 mmol) in dichloromethane (4 mL) and methanol (6 mL). The resulting mixture was stirred for 5 min and triphenylphoshine (200 mg, 0.75 mmol) was then added. The cold-bath was removed and stirring was continued for 1.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 19 cm), using 20% ethyl acetate-hexane, gave **133** (47 mg, 82%) as an pure [^{1}H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2922, 1751, 1729, 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.20-1.35 (m, 1 H), 1.39-1.90 (m, 5 H), 2.12-2.46 (m, 4 H), 2.50-2.67 (m, 2 H), 3.70 (s, 3 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 22.31, 24.45, 26.34, 31.21, 31.31, 34.19, 39.20, 44.48, 51.41, 51.90, 53.04, 215.50; exact mass, *m/z* calcd for $C_{13}H_{20}O_3$ 224.1412,

found 224.1411. An analytical sample was prepared by Kugelrohr distillation (85°C, 0.12 mm Hg). Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.41; H, 8.73.

(2*E*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-methanol and (2*Z*,3aα,7aβ)-Octahydro-2-(phenylmethylene)-3a*H*-indene-3a-methanol (136).



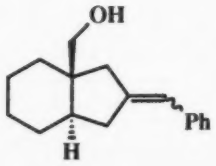
104 **136**

A solution of ester **104** (508 mg, 1.88 mmol) in THF (5 mL plus 2 mL rinse) was added dropwise to a stirred and cooled (ice-bath) suspension of lithium aluminum hydride (142 mg, 3.75 mmol) in THF (10 mL). The ice-bath was removed and stirring was continued for 5 h. The mixture was recooled to ca 0°C (ice-bath) and quenched by successive dropwise addition of water (0.14 mL), 15% sodium hydroxide (0.14 mL), and water (0.42 mL). The mixture was stirred for 10 min and filtered through a pad (2 x 5 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 15% ethyl acetate-hexane, gave **136** (433mg, 95%) as a pure [^{1}H NMR] colorless oil which was a mixture of two diastereomers in a 1:1 ratio (^{1}H NMR). The diastereomers were separated by flash chromatography. The

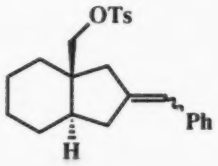
faster moving diastereomer (**136a**) had: FT-IR ($CHCl_3$ cast) 3324, 2926, 2848, 1442, 1030, 740, 692 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.05-1.23 (m, 2 H), 1.23-1.42 (m, 2 H), 1.42-1.74 (m, 4 H), 1.78-1.88 (m, 1 H) 2.03 (dd, *J* = 16.0, 2.5 Hz, 1 H), 2.11-2.30 (m, 2 H), 2.51 (ddd, *J* = 16.0, 7.5, 1.0 Hz, 1 H), 2.94 (d, *J* = 16.0 Hz, 1 H), 3.21 (d, *J* = 11.0 Hz, 1 H), 3.79 (d, *J* = 11.0 Hz, 1 H), 6.38 (m, 1 H), 7.10-7.20 (m, 1 H), 7.26-7.35 (m, 4 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 21.37, 24.84, 26.42, 33.03, 38.09, 42.19, 45.68, 47.24, 60.42, 123.66, 125.86, 128.03, 128.22, 138.65, 143.47; exact mass, *m/z* calcd for $C_{17}H_{22}O$ 242.1671, found 242.1675. An analytical sample was prepared by Kugelrohr distillation (125°C, 0.005 mm Hg). Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.39; H, 9.18.

The slower moving diastereomer (**136b**) had: FT-IR ($CHCl_3$ cast) 3328, 2925, 2848, 1442, 1030, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00-1.41 (m, 4 H), 1.46-1.90 (m, 5 H), 2.05-2.27 (m, 3 H), 2.68 (dd, J = 17.0, 8.0 Hz, 1 H), 2.75 (d, J = 16.0 Hz, 1 H), 3.29 (d, J = 11.0 Hz, 1 H), 3.83 (dd, J = 11.0, 2.0 Hz, 1 H), 6.40 (br s, 1 H), 7.10-7.20 (m, 1 H), 7.26-7.35 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.36, 25.06, 26.43, 32.62, 35.06, 44.25, 46.27, 48.70, 60.25, 123.38, 125.84, 127.96, 128.27, 138.61, 143.50; exact mass, *m/z* calcd for $C_{17}H_{22}O$ 242.1671, found 242.1667. An analytical sample was prepared by recrytallization from hexane (mp 91-93°C). Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.98; H, 8.87.

(2*E*,3aα,7aβ)-[Octahydro-2-(phenylmethylene)-3a*H*-inden-3a-yl]methyl 4-methylbenzenesulfonate and (2*Z*,3aα,7aβ)-[Octa-hydro-2-(phenylmethylene)-3a*H*-inden-3a-yl]methyl 4-methylbenzenesulfonate (137).



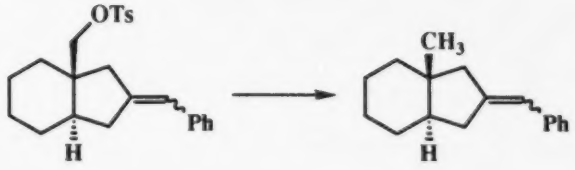
136



137

p-Toluenesulfonyl chloride (682 mg, 3.58 mmol) was added to a stirred and cooled (ice-bath) solution of alcohol **136** (433 mg, 1.79 mmol) in pyridine (7 mL). The resulting solution was allowed to stand in the fridge (ca 5°C) for 4 days. The mixture was poured onto ice and extracted with ether (3 x 30 mL). The combined ether extracts were washed with 10% HCl (2 x 10 mL), and water (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 17), using 10% ethyl acetate-hexane, gave a white solid (**137**) which was used directly in the next experiment without characterization.

***trans*-(2*E*)-Octahydro-3a-methyl-2-(phenylmethylene)-1*H*-indene and *trans*-(2*Z*)-Octahydro-3a-methyl-2-(phenylmethylene)-1*H*-indene (139).**



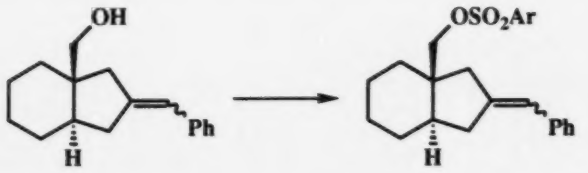
137 **139**

Lithium triethylborohydride (8.9 mL, 1.0 M in THF, 8.9 mmol) was added dropwise to a stirred and cooled (ice-bath) solution of tosylate **137** (1.79 mmol, assuming 100% conversion of the alcohol to the tosylate) in THF (5 mL). The cold bath was removed and the solution was refluxed for 15 h, cooled, quenched with 3N sodium hydroxide (20 mL), and extracted with ether (3 x 10 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was filtered through a pad (3 x 5 cm) of silica gel, using first pentane and then ethyl acetate. The pentane filtrate was evaporated and Kugelrohr distillation (90°C, 0.01 mm Hg) of the residue gave **139** (226 mg, 56%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1:1.4 ratio (^{1}H NMR): FT-IR ($CHCl_3$ cast) 2925, 2855, 1446, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.75 (s, 1.2 H), 0.80 (s, 1.8 H), 1.15-1.185 (m, 9 H), 2.07-2.73 (m, 4 H), 6.30-6.40 (m, 1 H), 7.08-7.20 (m, 1 H), 7.20-7.38 (m, 4 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 16.57, 17.03, 21.90, 25.32, 25.56, 26.63, 35.03, 37.99, 38.68, 39.13, 39.48, 40.98, 47.03,

47.88, 48.51, 51.82, 122.73, 123.00, 125.61, 127.89, 127.93, 128.13, 128.20, 138.85, 138.96, 144.54, 144.79; exact mass, *m/z* calcd for $C_{17}H_{22}$ 226.1721, found 226.1714. Anal. Calcd. for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.28; H, 9.58.

Evaporation of the ethyl acetate filtrate and flash chromatography of the residue over silica gel (2 x 18 cm), using 15% ethyl acetate-hexane, gave recovered alcohol **136** (182 mg, 42%).

(2*E*,3aα,7aβ)-[Octahydro-2-(phenylmethylene)-3a*H*-inden-3a-yl]methyl 2,4,6-tris-(1-methylethyl)benzenesulfonate and (2*Z*,3aα,7aβ)-[Octahydro-2-(phenylmethylene)-3a*H*-inden-3a-yl]methyl 2,4,6-tris-(1-methylethyl)benzenesulfonate (138).



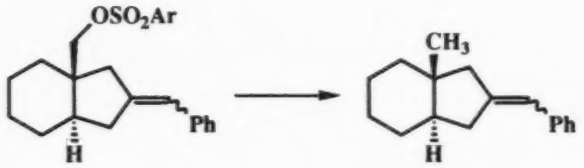
Ar = 2,4,6-triisopropylbenzene

136 **138**

2,4,6-Triisopropylbenzenesulfonyl chloride (606 mg, 2.00 mmol) was addded to a solution of alcohol **136** (162 mg, 0.67 mmol) in pyridine (5 mL). The solution was stirred at 80°C (oil bath temperature) overnight, cooled, poured onto ice and extracted with ether (3 x 30 mL). The combined ethereal extracts were washed with 10% HCl (2 x 15 mL) and water (15

mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 5% ethyl acetate-hexane, gave **138** (274 mg, 81%) a viscous oil which was not characterized but used directly in the next experiment.

***trans*-(2*E*)-Octahydro-3a-methyl-2-(phenylmethylene)-1*H*-indene and *trans*-(2*Z*)-Octahydro-3a-methyl-2-(phenylmethylene)-1*H*-indene (139).**



Ar = 2,4,6-triisopropylbenzene

138 **139**

Lithium triethylborohydride (2.7 mL, 1.0 M in THF, 2.7 mmol) was added dropwise to a stirred solution of sulfonate **138** (274 mg, 0.54 mmol) in THF (2 mL). The solution was refluxed for 12 h. Additional lithium triethylborohydride (1.1 mL, 1.0 M in THF, 1.1 mmol) was added and refluxing was continued for 12 h. The mixture was cooled, quenched with 3N sodium hydroxide (20 mL) and extracted with ether (3 x 20mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was filtered through a pad (4 x 4 cm) of silica gel with pentane. Evaporation of the filtrate gave **139** (115 mg, 94%) as a pure [^{1}H NMR] colorless oil, identical to material obtained from tosylate **137**.

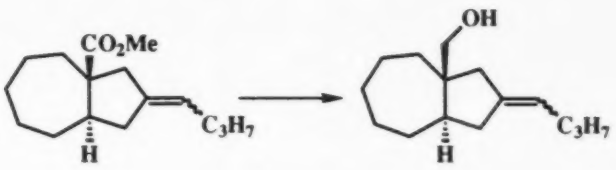
***trans*-Octahydro-3a-methyl-2*H*-inden-2-one (144).**

139 **144**

This experiment was done using the apparatus described by Rubin,[33] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a dry-ice acetone bath, was bubbled for 4 min into dry dichloromethane (19.6 mL) at -78°C. The resulting solution was transferred into the other bulb of the apparatus which contained a cold (-78°C) solution of **139** (54.1 mg, 0.24 mmol) in dichloromethane (4 mL) and methanol (6 mL). The resulting solution was stirred for 5 min and triphenylphosphine (188 mg, 0.72 mmol) was added. The cold-bath was removed and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm), using 50% dichloromethane-hexane, gave **144** (22 mg, 60%) as a pure [^{1}H NMR] colorless oil: FT-IR (CH_2Cl_2 solution) 2930, 2858, 1710, 1448, 1407, 1380, 1269, 1260, 1191, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.90 (s, 3 H), 1.25-1.98 (m, 10 H), 1.98-2.29 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.16, 21.69, 24.91, 26.48, 38.52, 39.03, 41.39, 45.73, 55.68, 218.67; exact mass, *m/z* calcd for $C_{10}H_{16}O$ 152.1201,

found 152.1204. A satisfactory combustion analysis could not obtained.

(2*E*,3aα,8aβ)-[2-Butylideneoctahydro-3a*H*-azulene]-3a-methanol and (2*Z*,3aα,8aβ)-[2-Butylideneoctahydro-3a*H*-azulene]-3a-methanol (145).

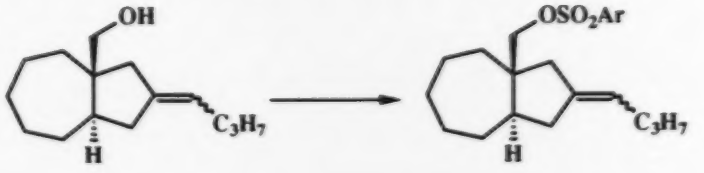


118 **145**

Ester **118** (171 mg, 0.68 mmol) in THF (3 mL plus 1 mL rinse) was added dropwise to a stirred and cooled (ice-bath) suspension of lithium aluminum hydride (54 mg, 1.4 mmol) in THF (3 mL). The cooling bath was removed and stirring was continued for 14 h. The reaction mixture was recooled to 0°C and quenched by successive dropwise addition of water (0.055 mL), 15% sodium hydroxide (0.055 mL), and water (0.165 mL). The mixture was stirred for 10 min more and filtered through a pad (2 x 3 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 17 cm), using 15% ethyl acetate-hexane, gave **145** (151 mg, 99%) as a pure [^{1}H NMR] colorless oil, which was a chromatographically (TLC) inseparable mixture of two isomers in a 1:1 ratio (^{1}H NMR): FT-IR (CH_2Cl_2 cast) 3334, 2955, 2922, 2858, 1465, 1452, 1377, 1035, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.87 (t, *J* =

7.5 Hz, 1.5 H), 0.88 (t, J = 7.5 Hz, 1.5 H), 0.96-1.13 (m, 1 H), 1.17-1.60 (m, 7 H), 1.60-2.20 (m, 10 H), 2.37-2.53 (m, 1 H), [2.55 (d, J = 16 Hz) and 2.69 (d, J = 17.0 Hz), 1 H], 3.40-3.52 (m, 1 H), 3.71 (br t, J = 10.5 Hz, 1 H), 5.10-5.26 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.89, 22.76, 22.90, 26.77, 26.82, 26.96, 27.05, 27.08, 27.36, 27.81, 31.49, 31.52, 36.68, 37.37, 37.93, 40.59, 41.76, 45.67, 46.38, 48.57, 48.80, 62.98, 63.24, 121.07, 121.09, 140.41, 140.52; exact mass, *m/z* calcd for $C_{15}H_{26}O$ 222.1984, found 222.1984. An analytical sample was prepared by Kugelrohr distillation (102°C, 0.005 mm Hg). Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.11; H, 11.98.

(2*E*,3aα,8aβ)-[2-Butylideneoctahydro-3a*H*-azulen-3a-yl]-methyl 2,4,6-tris(1-methylethyl)benzenesulfonate and (2*E*,3aα,8aβ)-[2-Butylideneoctahydro-3a*H*-azulen-3a-yl]methyl 2,4,6-tris(1-methylethyl)benzenesulfonate (146).

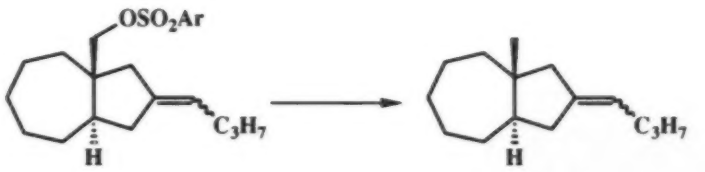


145 **146**

2,4,6-Triisopropylbenzenesulfonyl chloride (811 mg, 2.68 mmol) was added to a solution of alcohol **145** (198 mg, 0.89 mmol) in pyridine (5 mL) at room temperature. The resulting

solution was stirred at 90°C (oil bath temperature) for 6 h, cooled, and poured onto ice. The resulting mixture was extracted with ether (3 x 20 mL) and the combined ether extracts were washed with 10% hydrochloric acid (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using first hexane and then 5% ethyl acetate-hexane, gave **146** as a colorless oil (334 mg, 76%) which was used directly in the next experiment without characterization.

trans-(2_E_)-2-Butylideneoctahydro-3a-methyl-1_H_-azulene and _trans_-(2_Z_)-2-Butylideneoctahydro-3a-methyl-1_H_-azulene (147).



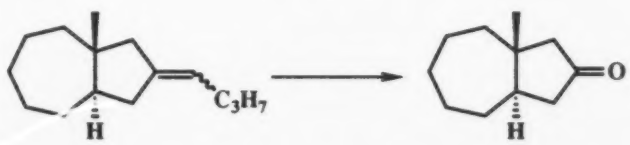
Ar = 2,4,6-triisopropylbenzene

146 **147**

Lithium triethylborohydride (3.4 mL, 1.0 M in THF, 3.4 mmol) was added dropwise to a stirred solution of sulfonate **146** (334 mg, 0.68 mmol) in THF (2 mL). The resulting solution was refluxed for 24 h. Additional lithium triethylborohydride (1.36 mL, 1.0 M in THF, 1.36 mmol) was added and refluxing was continued for another 24 h. The mixture was cooled, quenched with 3N sodium hydroxide (15 mL) and extracted with ether (3 x 20 mL). The combined ether

extracts were dried ($MgSO_4$) and evaporated. The crude residue was filtered through a pad (3 x 5 cm) of silica gel with hexane. The hexane filtrate was evaporated and Kugelrohr distillation (127°C, 17 mm Hg) of the residue gave **147** (102 mg, 73%) as a pure [^{1}H NMR] colorless oil, which was a chromatographically (TLC) inseparable mixture of two isomers in a 1.4:1 ratio (^{1}H NMR): FT-IR (CCl_4 cast) 2955, 2923, 2859, 1464, 1449, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.79 (s, 1.75 H), 0.82 (s, 1.25 H), 0.87 (t, J = 7.5 Hz, 3 H), 1.15-2.22 (m, 18 H), 2.30-2.45 (m, 1 H), 5.09-5.19 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.90, 18.11, 18.80, 22.88, 22.97, 24.18, 26.68, 26.76, 26.80, 26.87, 28.07, 28.50, 31.52, 36.39, 40.22, 43.02, 43.53, 43.79, 44.03, 46.22, 46.31, 48.31, 52.65, 120.46, 120.55, 141.09, 141.31; exact mass, *m/z* calcd for $C_{15}H_{26}$ 206.2034, found 206.2037. Anal. Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.26; H, 12.79.

trans-Octahydro-3a-methyl-2_H_-azulen-2-one (148).

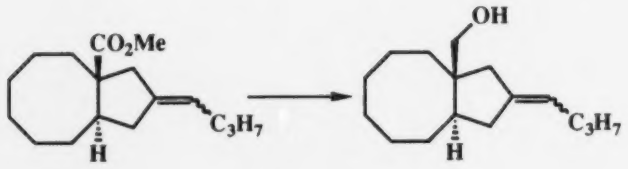


147 **148**

This experiment was done using the apparatus described by Rubin,[33] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a

dry-ice acetone bath, was bubbled for 4 min into dry dichloromethane (7.7 mL) at -78°C. The resulting solution was transfered into the other bulb of the apparatus which contained a cold (-78°C) solution of **147** (19.4 mg, 0.094 mmol) in dichloromethane (2 mL) and methanol (2.5 mL). The resulting mixture was stirred for 5 min and dimethyl disulfide (0.5 mL) was added. The cold-bath was removed and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 5% ethyl acetate-hexane gave **148** (8.0 mg, 50%) as a pure [^{1}H NMR] oil: FT-IR (CH_2Cl_2 cast) 2923, 2858, 1744, 1448, 1402, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.95 (s, 3 H), 1.25-1.90 (m, 10 H), 1.95 (dd, J = 18.0, 12.0 Hz, 1 H), 2.10 (s, 2 H), 2.13-2.23 (m, 1 H), 2.32 (dd, J = 18.0, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 18.56, 26.43, 26.80, 28.19, 42.48, 43.41, 43.77, 44.99, 57.90, 218.98; exact mass, *m/z* calcd for $C_{11}H_{18}O$ 166.1358, found 166.1355. A satisfactory combustion analysis could not be obtained.

(2*E*,3aα,9aβ)-[2-Butylidenedecahydro-3a*H*-cyclopenta-cyclooctene]-3a-methanol and (2*Z*,3aα,9aβ)-[2-Butylidenedecahydro-3a*H*-cyclopentacyclooctene]-3a-methanol (149).

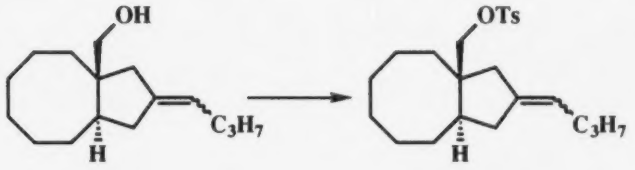


121 **149**

Ester **121** (302 mg, 1.14 mmol) in THF (5 mL plus 1 mL rinse) was added dropwise to a stirred and cooled (ice-bath) suspension of lithium aluminum hydride (92 mg, 2.3 mmol) in THF (3 mL). The ice-bath was removed and stirring was continued for 20 h. The reaction was quenched by successive dropwise addition of water (0.09 mL), 15% sodium hydroxide (0.09 mL), and water (0.30 mL). The mixture was stirred for 20 min and filtered through a pad (2 x 3 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10% ethyl acetate-hexane, gave **149** (269 mg, 100%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in about a 1:1 ratio (^{13}C NMR): FT-IR (CCl_4 cast) 3330, 2923, 2860, 1470, 1449, 1045, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.20-2.06 (m, 18 H), 2.10-2.46 (m, 4 H), 3.40-3.63 (m, 2 H), 5.16-5.28 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.92, 22.21, 22.77, 22.90, 25.76,

26.57, 29.62, 29.97, 31.47, 31.55, 32.34, 32.40, 34.41, 34.84, 36.32, 39.50, 39.55, 39.94, 40.07, 44.34, 46.03, 46.25, 66.36, 66.55, 121.47, 121.63, 139.39, 139.53; exact mass; *m/z* calcd for $C_{16}H_{28}O$ 236.2140, found, 236.2143. Anal. Calcd. for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.33; H, 12.03.

(2*E*,3aα,9aβ)-[2-Butylidenedecahydro-3a*H*-cyclopentacycloocten-3a-yl]methyl 4-methylbenzenesulfonate and (2*Z*,3aα,9aβ)-[2-Butylidenedecahydro-3a*H*-cyclopentacycloocten-3a-yl]methyl 4-methylbenzenesulfonate (150).

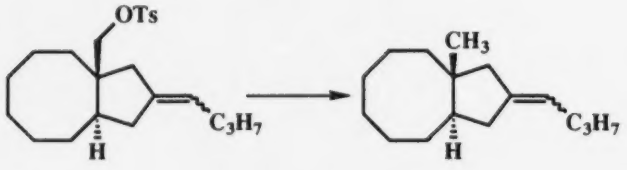


149 **150**

p-Toluenesulfonyl chloride (384 mg, 2.0 mmol) was added to a solution of alcohol **149** (238 mg, 1.0 mmol) in pyridine (5 mL) at 0°C (ice-bath). Stirring was continued for 24 h, the cooling bath being allowed to attain room temperature. The mixture was poured onto ice and extracted with ether (3 x 25 mL). The combined ether extracts were washed with 10% HCl (2 x 10 mL), and water (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 5% ethylacetate-hexane, gave the product as a

viscous oil which was used direclty in the next experiment without characterization.

trans-(2_E_)-2-Butylidenedecahydro-3a-methyl-1_H_-cyclopentacyclooctene and _trans_-(2_Z_)-2-Butylidenedecahydro-3a-methyl-1_H_-cyclopentacyclooctene (151).

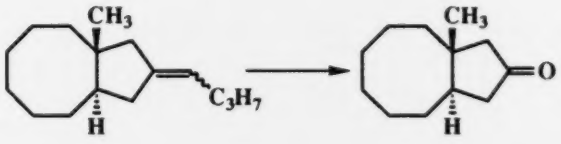


150 **151**

Lithium triethylborohydride (5.0 mL, 1.0 M in THF, 5.0 mmol) was added dropwise to a stirred solution of tosylate **150** (1.0 mmol, assuming 100% conversion of the alcohol into the tosylate) in THF (2 mL). The resulting solution was refluxed for 17 h. An additional quantity of lithium triethyl borohydride (6.0 mL, 1.0 M in THF, 6.0 mmol) was added and refluxing was continued for another 48 h. The mixture was cooled, quenched with 3 N sodium hydroxide (20 mL) and extracted with ether (3 x 20 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was filtered through a pad (3 x 5 cm) of silica gel, using first hexane (100 mL) and then ethyl acetate (100 mL). The hexane filtrate was evaporated and the residue chromatographed over silica gel (three times) (2 x 16 cm), using 100% hexane, to give **151** (21 mg, 9%) as a pure [^{1}H NMR] colorless oil which was a chromatographically (TLC)

inseparable mixture of two isomers in a 1.5:1 ratio (^{1}H NMR): ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.76 (d, J = 0.7 Hz, 1.8 H) 0.79 (s, 1.2 H], 0.88 (t, J = 7.5 Hz, 1.2 H), 0.89 (t, J = 7.5 Hz, 1.8 H), 1.24-1.82 (m, 15 H), 1.84-2.40 (m, 6 H), 5.10-5.23 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.91, 20.54, 21.16, 22.52, 22.87, 22.96, 25.63, 26.41, 29.80, 30.18, 31.47, 31.53, 32.31, 32.35, 36.01, 39.63, 40.05, 41.46, 41.71, 46.13, 50.18, 120.87, 121.07, 140.19, 140.40. A satisfactory combustion analysis could not be obtained.

trans-Decahydro-3a-methyl-2_H_-cyclopentacycloocten-2-one (152).

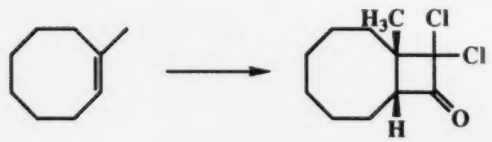


151 **152**

The procedure employed for **133** was followed using dichloromethane (7.5 mL), alkene **151** (20 mg, 0.09 mmol) in dichloromethane (2 mL) and methanol (2.5 mL), and dimethyl sulfide (0.5 mL) in place of triphenylphosphine. Flash chromatography of the crude product over silica gel (2 x 15 cm), using 5% ethyl acetate-hexane, gave **152** (11 mg, 65%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2922, 1751, 1729, 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.94 (d, J = 0.8 Hz, 3 H), 1.30-1.94 (m, 13 H), 2.05 (ddd, J = 18.5, 12.5, 1.5 Hz, 1 H), 2.23 (d, J = 16.5 Hz, 1 H), 2.31 (d, J = 18.0 Hz, 1 H), 2.30-

2.46 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 21.07, 22.27, 25.35, 26.16, 29.77, 32.02, 39.51, 40.62, 44.48, 55.77, 218.59.

cis-10,10-Dichloro-1-methylbicyclo[6.2.0]decan-9-one (153).



153

A solution of trichloroacetyl chloride (1.17 mL, 10.5 mmol) and phosphorus oxychloride (0.98 mL, 10.5 mmol) in ether (10 mL) was added dropwise over 1 h to a stirred suspension of activated zinc copper couple (0.72 g) and 1 methylcycloocetene[34] (1.25 g, 10.1 mmol) in ether (20 mL). The resulting suspension was then refluxed for 24 h, cooled and filtered through a pad (2 x 5 cm)of Celite with ether (30 mL). The filtrate was evaporated to approximately 25% of its original volume and diluted with an equal volume of pentane. The solution was stirred for a few minutes to precipitate the zinc salts, then decanted from the dark brown residue, washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), and evaporated. Flash chromatography of the residue over silica gel (4 x 16 cm), using 10% dichloromethane-hexane, gave **153** (904 mg, 38%) as a pure [^1H NMR] colorless oil: ^1H NMR ($CDCl_3$ 200 MHz) δ 1.05-1.38 (m, 3H), 1.40 (s, 3H), 1.50-2.32 (m, 9H), 3.84 (dd, J = 6.5, 2.5

Hz, 1H). The material was used directly in the next step without full characterization.

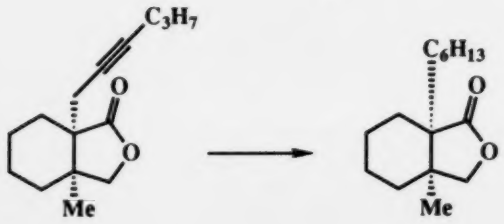
cis-Decahydro-3a-methyl-2_H_-cyclopentacycloocten-2-one (154).

153 **154**

Ethereal diazomethane (30 mL, 0.2 M, ca 6.0 mmol) was added to **153** (0.9000 g, 3.8 mmol) followed by methanol (2 mL). The solution was stirred for 12 h, the remaining diazomethane was destroyed with a few drops of acetic acid, and the solvent was evaporated. Flash chromatography of the residue over silica gel (4 x 16 cm), using 10% dichloromethane-hexane, gave the ring expansion product. This was dissolved in acetic acid (5 mL) and Zn powder (1 g) was added. The stirred mixture was heated for 2 h at 65°C, cooled and filtered through a pad (2 x 5 cm) of Ccelite with ethyl acetate (70 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 5% ethyl acetate-hexane, gave **154** (196 mg, 28%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2920, 2855, 1744, 1467, 1445, 1404, 1378, 1165, 514 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.08 (s, 3 H), 1.20-1.50 (m, 6 H), 1.60-2.20 (m, 10 H), 2.75 (ddd, J = 21.0, 9.0, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$

75.5 MHz) δ 24.67, 25.38, 25.58, 25.84, 31.31, 33.30, 33.44, 41.48, 45.25, 49.46, 52.42, 219.74; exact mass *m/z* calcd for $C_{12}H_{20}O$ 180.15. Found: 180.1515. Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.01; H, 11.35.

cis-7a-Hexylhexahydro-3a-methyl-1(3*H*)-isobenzofuranone (155).



107 **155**

Palladium (10 mg, 5% on carbon) was added to a solution of acetylene **107** (96 mg, 0.41 mmol) in ethyl acetate (2 mL). The flask was flushed with hydrogen and the suspension was stirred under a hydrogen atmosphere (balloon) for 8 h. The mixture was filtered through a pad (3 x 2 cm) of Celite and the pad was washed with ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 14 cm), using 8% ethyl acetate-hexane, gave **155** (94 mg, 96%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2932, 2859, 1773, 1106, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.87 (t, *J* = 7.0 Hz, 3 H), 1.06 (s, 3 H), 1.10-1.44 (m, 12 H), 1.44-1.64 (m, 5 H), 2.06-2.20 (m, 1 H), 3.76 (d, *J* = 8.5 Hz, 1 H), 3.99 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz)

δ 14.06, 16.81, 21.38, 22.63, 23.23, 23.52, 27.82, 29.99, 31.66, 33.50, 36.35, 41.30, 48.44, 75.91, 180.04.

Ethyl *cis*-2-Hexyl-2-hydroxy-1-methylcyclohexane-carboxylate and Ethyl *trans*-2-Hexyl-2-hydroxy-1-methylcyclohexanecarboxylate (157).

156 **157**

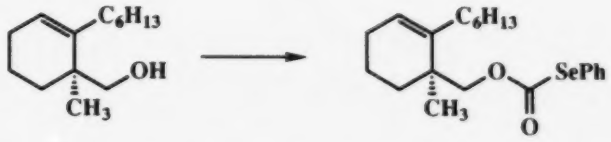
A solution of bromohexane (2.4 mL, 16.8 mmol) in THF (15 mL) was added dropwise to a stirred suspension of Mg turnings (490 mg, 20.2 mmol) in THF (5 mL). The mixture was then refluxed for 2 h, cooled to 0°C (ice-bath) and added by cannula to a stirred and cooled (-78°C) solution of ketoester **156** (2.500 g, 14.0 mmol) in THF (20 mL). The resulting solution was stirred at -78°C for 1 h and the cold bath was then removed. After ca 30 min the mixture was quenched with saturated aqueous ammonium chloride (10 mL), extracted with ether (3 x 40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 5% ethyl acetate-hexane, gave **157** (2.15 g, 59%) as a colorless oil: (^{1}H NMR 80 MHz) δ 0.7-2.2 (m, 27 H), 3.0 (s, 1 H), 4.23 (q, J = 5.2 Hz, 2 H). The material was used directly in the next step without further characterization.

(2-Hexyl-1-methylcyclohex-2-ene)methanol (159) and (2-Hexylidene-1-methylcyclohexyl)methanol.

157 **159**

p-Toluenesulfonic acid monohydrate (60 mg, 0.32 mmol) was added to a solution of alcohol **157** (1.76 g, 6.5 mmol) in xylene (65 mL). The solution was refluxed for 1 h. The condenser was removed and replaced by a set-up for distillation, and most of the xylene was distilled. Solid sodium carbonate (500 mg) was added to the residue which was then filtered through a pad (4 x 5 cm) of silica gel, and the filtrate was evaporated. The crude product in THF (5 mL) was added dropwise to a stirred and cooled (ice-bath) suspension of lithium aluminum hydride (260 mg, 6.5 mmol) in THF (10 mL). The ice-bath was removed and stirring was continued for 1.5 h. The reaction was quenched by successive dropwise addition of water (0.26 mL), 15% sodium hydroxide (0.26 mL), and water (0.78 mL). The mixture was stirred for 15 min and filtered through a pad (2 x 5 cm) of Celite . The pad was washed with ether (75 mL) and the filtrate was evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 10% ethyl acetate-hexane, gave a mixture of **159** and the corresponding hexylidene derivative (1.20 g, 88%). This material was used directly for the next step.

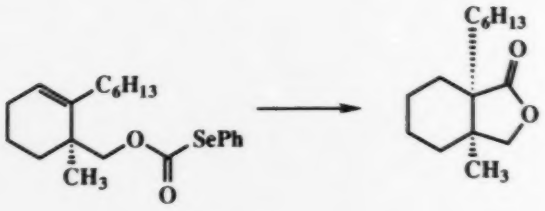
Se Phenyl-*O*-[(2-hexyl-1-methylcyclohex-2-en-1-yl)-methyl]carbonoselenoate (160) and Se Phenyl-*O*-[(2-hexylidene-1-methylcyclohex-1-yl)methyl]carbono-selenoate.



159 **160**

A solution of alcohol **159** (1.14 g, 5.4 mmol) and triethylamine (0.91 mL, 6.5 mmol) in THF (20 mL) was added dropwise to an excess of phosgene (ca 2 mL) at -78°C. The cold bath was removed and the reaction mixture was stirred for 30 min. The mixture was then concentrated under reduced pressure to approximately half its original volume, and a solution of benzeneselenol (0.75 mL, 7.0 mmol) and pyridine (0.52 mL, 6.5 mmol) in THF (8 mL) was added. The mixture was stirred at room temperature for 45 min, quenched with water (15 mL) and extracted with ether (3 x 25 mL). The combined ether extracts were washed with brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 5% dichloromethane-hexane, gave **160** (1.97 g, 93%) as a colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 2.8:1 ratio (^1H NMR). The material was used directly in the next and final step of the sequence.

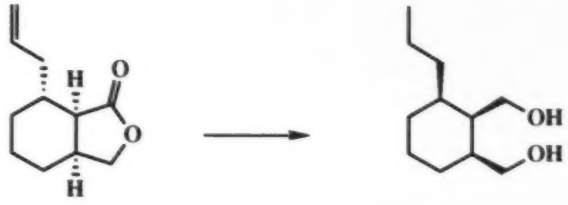
cis-7a-Hexylhexahydro-3a-methyl-1(3_H_)-isobenzofuranone (161).



160 **161**

Triethylborane (1.0 mL, 1.0 M in hexane, 1.0 mmol) was added to a solution of selenide **160** (398 mg, 1.01 mmol) and triphenyltin hydride (532 mg, 1.2 mmol) in hexane (100 mL) at room temperature (protection from moisture by a drying tube packed with Drierite). After 24 h the solvent was evaporated and flash chromatography of the residue over silica gel (4 x 16 mm), using 8% ethyl acetate-hexane, gave **161** (223 mg, 92%) as a colorless oil: FT-IR (CCl_4 cast) 2932, 2859, 1773, 1106, 1012 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.05 (s, 3 H), 1.10-1.65 (m, 17 H), 2.07-2.16 (m, 1 H), 3.76 (d, J = 8.5 Hz, 1 H), 4.00 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.06, 16.81, 21.38, 22.63, 23.23, 23.52, 27.82, 29.99, 31.66, 33.49, 36.35, 41.30, 48.43, 75.91, 180.04.

(1R*,2S*,3S*)-(±)-(2-Hydroxymethyl-3-propylcyclohexane)methanol (163).



126 **163**

Palladium (2.0 mg, 5% on carbon) was added to a solution of olefin **126** (17 mg, 0.094 mmol) in ethyl acetate (1 mL). The flask was flushed with hydrogen and the suspension was stirred under a hydrogen atmosphere (balloon) for 20 h. The mixture was filtered through a pad (3 x 2 cm) of Celite and the pad was washed with ether. Lithium aluminum hydride (10 mg, 0.25 mmol) was added to a solution of the residue dissolved in tetrahydrofuran and the mixture stirred at room temperature for 3 h. The reaction was quenched by successive dropwise addition of water (0.01 mL), 15% sodium hydroxide (0.01 mL), and water (0.03 mL). The mixture was stirred for 20 min and filtered through a pad (2 x 3 cm) of Celite. The pad was washed with ether and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 14 cm), using 60% ethyl acetate-hexane, gave **163** (14.5 mg, 83%) as a pure [^{1}H NMR] colorless oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.10-1.72 (m, 12 H), 1.95-2.05 (m, 1 H), 3.20 (s, 2 H), 3.50-3.66 (m, 2 H), 3.74-3.94 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.44, 20.05,

21.28, 27.72, 28.91, 34.95, 35.05, 37.81, 44.13, 63.79, 65.04.

(1R*,2S*,3S*)-(±)-[(2-Acetoxymethyl-3-propylcyclohexane-1-yl)methyl] acetate (164).

163 **164**

Acetic anhydride (0.022 mL, 0.23 mmol) was added to a solution of diol **163** (14.5 mg, 0.078 mmol) and 4-*N*,*N*-dimethylaminopyridine (2 mg, 0.016 mmol) in pyridine (1.0 mL). The mixture was stirred for 4.5 h at room temperature, quenched by addition of saturated ammonium chloride (5 mL), and extracted with ether (2 x 15 mL). The combined ether extracts were washed with 2 M aqueous hydrochloric acid (2 x 5 mL), and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 14 cm), using 15% ethyl acetate-hexane, gave **164** (18.8 mg, 89%) as a pure [^{1}H NMR] colorless oil: FT-IR (CH_2Cl_2 cast) 2958, 2925, 2853, 1744, 1257, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.90 (s, 3 H), 1.16-1.68 (m, 11 H), 1.79-1.88 (m, 1 H), 2.05 [s, 6 H], 2.10-2.20 (m, 1 H), 4.00-4.21 (m, 4 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 13.98, 19.80, 20.19, 20.62, 25.89, 27.51, 33.72, 34.29, 34.57, 39.99, 64.24, 65.27, 170.66.

(1R*,2S*,3S*)-(±)-(2-Hydroxymethyl-3-propylcyclohex-4-ene)methanol (167).

165 **167a**

Maleic anhydride (630 mg, 6.4 mmol) was added to a solution of diene **165**[30] (517 mg, 5.4 mmol) in benzene (5 mL) and the solution was refluxed for 3.5 h, cooled, and then concentrated under reduced pressure to give a waxy solid which was taken up in THF (20 mL). Lithium aluminum hydride (520 mg, 13 mmol) was added in small portions over 10 min (stirring) and the resulting suspension was refluxed for 24 h. The mixture was cooled to room temperature and quenched by successive dropwise addition (stirring) of water (0.5 mL), 15% sodium hydroxide (0.5 mL), and water (1.5 mL). Stirring was continued for 20 min and the mixture was filtered through a pad (2 x 4 cm) of Celite. The pad was washed with ethyl acetate (100 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (4 x 14 cm), using 70% ethyl acetate-hexane, gave **167a** (690 mg, 70%) as a colorless oil: FT-IR (CH_2Cl_2 cast) 3299, 2957, 2928, 2896, 2873, 1655, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J = 7.0 Hz, 3 H), 1.20-1.50 (m, 4 H), 1.90-2.10 (m, 4 H),

2.10-2.40 (m, 1 H), 3.25 (br s, 1 H), 3.50-3.79 (m, 4 H), 5.40 (br d, J = 10 Hz, 1 H), 5.54-5.66 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.23, 20.49, 24.75, 35.30, 39.67, 40.53, 41.33, 57.83, 65.90, 125.87, 130.52; exact mass, m/z calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1458.

(1R*,2S*,3S*)-(±)-[(2-Acetoxymethyl-3-propylcyclohex-4-ene-1-yl)methyl] acetate (167b).

167a **167b**

Acetic anhydride (0.17 mL, 1.8 mmol) was added to a solution of diol **167a** (110 mg, 0.6 mmol) and 4-*N*,*N*-dimethylaminopyridine (10 mg, 0.08 mmol) in pyridine (1.5 mL). The mixture was stirred for 5 h at room temperature, quenched by addition of saturated ammonium chloride (10 mL), and extracted with ether (2 x 15 mL). The combined ether extracts were washed with 2 M aqueous hydrochloric acid (2 x 5 mL), and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 15% ethyl acetate-hexane, gave **167b** (127 mg, 79%) as a pure [^1H NMR] colorless oil: FT-IR ($CHCl_3$ cast) 2958, 2924, 1742, 1369, 1235, 1037 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.93 (t, J = 7.0 Hz, 3 H), 1.20-1.50 (m, 4 H), 1.74-1.90 (m,

1 H), 2.00-2.30 [m, including singlets at δ 2.04 and δ 2.07, 9 H], 3.92-4.20 (m, 4 H), 5.45 (br d, J = 10.0 Hz, 1 H), 5.58-5.67 (m, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.18, 20.43, 20.96, 21.08, 25.87, 34.99, 35.86, 37.65, 39.54, 61.20, 67.42, 125.17, 130.47, 171.05; exact mass, m/z calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1776. Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.08; H, 9.23.

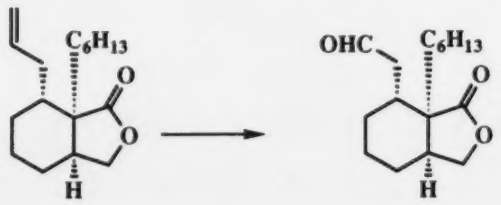
(1R*,2S*,3S*)-(±)-[(2-Acetoxymethyl-3-propylcyclohexyl)methyl] acetate (168).

167b **168**

Palladium (10 mg, 5% on carbon, 0.005 mmol) was added to a solution of olefin **167b** (120 mg, 0.45 mmol) in ethyl acetate (5 mL). The flask was flushed with hydrogen and the suspension was stirred under a hydrogen atmosphere (balloon) for 4 h. The mixture was filtered through a pad (2 x 4 cm) of Celite and the pad was washed with ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 14 cm), using 15% ethyl acetate-hexane, gave **168** (121 mg, 100%) as a pure (TLC) colorless oil: FT-IR (CH_2Cl_2 cast) 2927, 1741, 1369, 1244, 1037 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.84-1.10 [m, including t at δ 0.90

(t, J = 7.0 Hz), 4 H], 1.10-1.40 (m, 6 H), 1.40-1.63 (m, 3 H), 1.74-1.96 (m, 2 H), 1.96-2.14 [m, including singlets at δ 2.02 and δ 2.05, 7 H], 3.92 (dd, J = 17.5, 7.5 Hz, 1 H), 4.01-4.18 (m, 3 H); ^{13}C NMR ($CDCl_3$ 50.3 MHz) δ 14.31, 20.47, 20.97, 21.10, 24.41, 25.78, 28.28, 36.50, 38.15, 40.81 (x 2), 60.76, 67.54, 171.09 (two signals); mass (CI), *m/z* calcd for $C_{15}H_{26}O_4$ 270, found 271. Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.39; H, 9.81.

(3aα,7α,7aα)-7a-Hexylhexahydro-7-(2-oxoethyl)-1(3*H*)-isobenzofuranone (169).

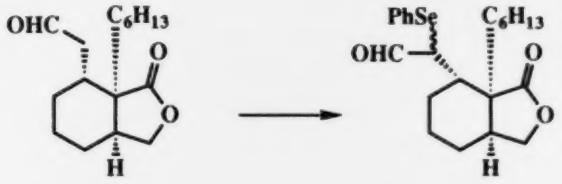


127 **169**

Ozone, precooled by passage through a glass coil immersed in a dry-ice acetone bath, was bubbled through a cold (-78°C) solution of alkene **127** (633 mg, 2.4 mmol) in dichloromethane (50 mL). After the starting material had been consumed (6.5 min, TLC control), dimethyl sulfide (0.5 mL) was added and the resulting solution was stirred overnight at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 13 cm), using 15% ethyl acetate-hexane, gave **169** (356 mg, 55%) as a pure [TLC] colorless oil: ^1H NMR ($CDCl_3$ 200 MHz) δ

0.89 (t, J = 6.0 Hz, 3 H), 1.00-1.43 (m, 9 H), 1.43-1.75 (m, 7 H), 2.19-2.40 (m, 2 H), 2.58-3.00 (m, 2 H), 4.21 (d, J = 10.0 Hz, 2 H), 9.71 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.06, 20.68, 20.99, 22.59, 24.84, 26.50, 26.59, 29.79, 31.54, 31.71, 36.42, 44.33, 46.67, 67.28, 179.91, 201.03.

(3aα,7α,7aα)-7a-Hexylhexahydro-7-[2-oxo-1-(phenylseleno)ethyl]-1(3*H*)-isobenzofuranone (170).

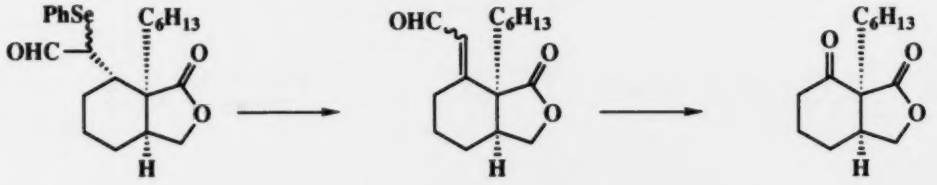


169 **170**

Concentrated hydrochloric acid (1 drop) was added to a stirred solution of aldehyde **169** (104 mg, 0.39 mmol) and phenylselenyl chloride (90 mg, 0.47 mmol) in ethyl acetate (4 mL). The mixture was stirred at room temperature for 9 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 15% ethyl acetate-hexane, gave unreacted aldehyde **169** (38 mg, 37%) and selenide **170** (96 mg, 60%, 93% corrected for recovered starting material) as a pure [^1H NMR] colorless oil which was a chromatographically (TLC) inseparable mixture of two isomers in a 1.4:1 ratio (^1H NMR): FT-IR (CCl_4 cast) 2928, 2857, 1761, 1705, 1107, 1021, 741 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ

0.80-0.94 (m, 3 H), 1.00-2.00 (m, 16 H), 2.26-2.35 (m, 0.4 H), 2.51 (dt, J = 21.5, 2.5 Hz, 0.6 H), 2.65-2.80 (m, 1 H), 4.07-4.26 (m, 3 H) 7.25-7.70 (m, 5 H), 9.36 (d, J = 2.0 Hz, 0.6 H), 9.52 (d, J = 6.0 Hz, 0.4 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.02, 14.09, 20.98, 21.09, 21.12, 21.75, 22.53, 22.62, 23.17, 25.06, 25.13, 25.96, 27.64, 27.71, 29.54, 29.82, 31.64, 31.68, 34.10, 36.40, 26.80, 42.76, 47.69, 48.87, 52.81, 54.71, 67.11, 67.28, 127.10, 127.75, 128.77, 128.90, 129.51, 129.67, 134.66, 135.02, 191.10, (191.89); exact mass, *m/z* calcd for $C_{22}H_{30}O_3Se$ 422.1360, found 422.1359. An analytical sample was prepared by Kugelrohr distillation (150-155°C, 0.20 mm Hg). Anal. Calcd. for $C_{22}H_{30}O_3Se$: C, 62.70; H, 7.17; O. 11.39. Found: C, 62.80; H, 7.00; O, 11.14.

cis-7a-Hexyltetrahydro-7-oxo-1(3_H_)-isobenzofuranone (171).



170 **171**

3-Chloroperoxybenzoic acid (100 mg, 80-85%, 0.48 mmol) was added to a stirred solution of selenide **170** (126 mg, 0.30 mmol) in dichloromethane (4 mL) at room temperature. After 20 min the mixture was quenched by addition of saturated

aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 14 cm), using 20% ethyl acetate-hexane, gave the unsaturated aldehyde (58 mg, 74%) as a mixture of two isomers which were oxidized directly without characterization.

Ozone, precooled by passage through a glass coil immersed in an dry-ice acetone bath was bubbled through a cold (-78°C) solution of the above unsaturated aldehyde (58 mg, 0.22 mmol) in dichloromethane-methanol (4:1, 25 mL) until a blue color appeared (2 min). Dimethyl sulfide (4 mL) was added and the solution was stirred overnight at room temperature. Evaporation of the solvents and flash chromatography of the residue over silica gel (2 x 15 cm), using 20% ethyl acetate-hexane, gave **171** (28 mg, 54%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2954, 2927, 2859, 1781, 1769, 1712, 1206, 1189, 1162, 1095, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.87 (t, J = 6.0 Hz, 3 H), 1.15-1.50 (m, 8 H), 1.60-2.15 (m, 6 H), 2.25-2.60 (m, 2 H), 2.78-2.93 (m, 1 H), 4.02 (dd, J = 9.5, 6.0 Hz, 1 H), 4.34 (dd, J = 9.5, 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.02, 22.38, 22.54, 24.92, 29.49, 31.49, 32.01, 39.23, 42.09, 60.27, 69.56, 174.47, 205.30; exact mass, m/z calcd for $C_8H_{10}O_3$ (M - C_6H_{12}) 154.0624, found 154.0631. An analytical sample was prepared by Kugelrohr distillation (120-122°C, 0.50 mm Hg). Anal.

Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.62; H, 9.04.

cis-7a-Hexyltetrahydro-7-oxo-1(3_H_)-isobenzofuranone, ethylene dithioacetal (172).

171 **172**

Boron trifluoride etherate (37 µL, 0.30 mmol) was added to a stirred and cooled (0°C) solution of ketone **171** (48 mg, 0.20 mmol) and 1,2-ethanedithiol (34 µL, 0.40 mmol) in dichloromethane (3 mL). The cold-bath was removed and the solution was stirred for 2 h. More 1,2-ethanedithiol (15 µL, 0.12 mmol) was added and, after 2 h, the mixture was quenched with aqueous sodium hydroxide (5 mL, 2.5 M) and extracted with dichloromethane (10 mL). The organic extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10% ethyl acetate-hexane, gave **172** (49 mg, 77%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2923, 1757, 1023, 997 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.20-1.39 (br s, 8 H), 1.54-1.85 (m, 5 H), 2.20-2.30 (m, 3 H), 2.64-2.75 (m, 1 H), 3.05-3.15 (m, 1 H), 3.23-3.33 (m, 3 H), 4.17-4.27 (m, 2 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ

14.06, 20.90, 22.24, 22.60, 26.60, 29.74, 31.64, 34.83, 37.93, 38.98, 39.93, 41.61, 54.18, 68.42, 71.77, 177.34; exact mass, *m/z* calcd for $C_{16}H_{26}O_2S_2$ 314.1374, found 314.1373.

cis-7a-Hexyl-(3,3a,4,5)-tetrahydro-1-isobenzofuranone (173).

172 **173**

Raney nickel (W-2, suspension in EtOH, settled volume 0.6 mL) was added to a solution of ketal **172** (35 mg, 0.11 mmol) in ethanol (4 mL) and benzene (0.3 mL). The suspension was refluxed for 20 h, cooled, and filtered through a pad (2 x 4 cm) of Celite. The pad was washed with ethyl acetate and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 5% ethyl acetate-hexane, gave olefin **173** (18 mg, 73%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2953, 2932, 2858, 1767, 1194, 1180, 1107, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.17-1.44 (br s, 8 H), 1.57-1.70 (m, 3 H), 1.70-1.85 (m, 1 H), 1.98-2.10 (m, 2 H), 2.55-2.66 (m, 1 H), 3.98 (dd, J = 9.0, 7.5 Hz, 1 H), 4.33 (dd, J = 9.0, 7.5 Hz, 1 H), 5.54 (dt, J = 10.0, 4.0 Hz, 1 H), 5.94 (dt, J = 10.0, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.07, 20.94,

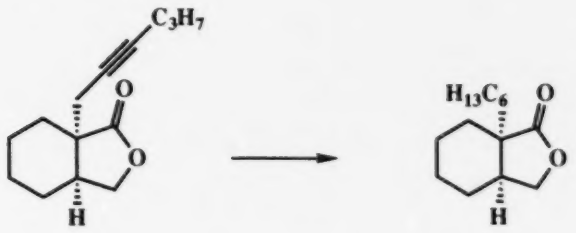
21.27, 22.60, 24.42, 29.60, 31.67, 36.31, 37.41, 46.93, 68.72, 126.49, 129.39, 179.62; exact mass, *m/z* calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1611.

cis-7a-Hexylhexahydro-1(3*H*)-isobenzofuranone (174).

173 **174**

Palladium (4 mg, 5% on carbon) was added to a solution of olefin **173** (18 mg, 0.08 mmol) in ethyl acetate (3 mL) at room temperature. The flask was flushed with hydrogen and the suspension was stired under a hydrogen atmosphere (balloon) for 4 h. The mixture was filtered through a pad (2 x 4 cm) of Celite and the pad was washed with ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 17 cm), using 10% ethyl acetate-hexane, gave **174** (16 mg, 91%) as a pure [^{1}H NMR] colorless oil: FT-IR (CCl_4 cast) 2931, 2858, 1769, 1451, 1204, 1113, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.20-1.95 (m, 18 H), 2.26-2.36 (m, 1 H), 3.95 (dd, J = 9.0, 5.0 Hz, 1 H), 4.30 (dd, J = 9.0, 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$ 75.5 MHz) δ 14.07, 22.10, 22.36, 22.60, 24.10, 25.80, 29.63, 29.73, 31.68, 34.93, 38.66, 38.90, 45.30, 69.50, 180.82; exact mass, *m/z* calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1776.

cis-7a-Hexylhexahydro-1(3_H_)-isobenzofuranone (175).



101 **175**

Palladium (4 mg, 5% on carbon) was added to a solution of alkyne **101** (22.6 mg, 0.10 mmol) in ethyl acetate (1.5 mL) at room temperature. The flask was flushed with hydrogen and the suspension was stired under a hydrogen atmosphere (balloon) for 4 h. The mixture was filtered through a pad (2 x 3 cm) of Celite and the pad was washed with ethyl acetate. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 7% ethyl acetate-hexane, gave **175** (17.7 mg, 77%) as a pure [^{1}H NMR] colorless oil identical to **174**.

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